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BRAIN TUMORS IN CHILDREN

I. GENERAL CONSIDERATIONS

A. EARL WALKER, M.D.,* BALTIMORE, MD., AND
THERON L. HOPPLE, M.D., TOLEDO, OHIO

INTRODUCTION

INTRACRANIAL tumors in childhood are now recognized as not infrequent occurrences. The clinical symptomatology, pathologic anatomy, and biologic course of such growths differ from those of brain tumors in adults. This is common knowledge to neurosurgeons but not so well known by physicians in general. Since the life history of these tumors was so clearly presented by Bailey, Buchanan, and Bucy[1] in 1939, certain modifications have been made in their diagnosis and treatment, which warrant a current review of the subject.

This series consists of patients whose symptoms of brain tumor began before their sixteenth birthday. The entire 100 cases presented in this paper have been observed by one of the authors at either the University of Iowa Hospitals, the University of Chicago Clinics, or The Johns Hopkins Hospital. In the majority of cases the patients have been under his treatment, but in a few instances in which operations did not seem advisable, the case came under study at necropsy. The 100 cases in this series have been proved to be tumors by visual verification, and in all but seven instances by histologic examination of biopsy or autopsy tissue. The error introduced by including the few cases which have not been biopsied would seem less than the statistical distortion resulting from their exclusion.

The age distribution curve of tumors in childhood in most series of cases has had an elevation at or about the 5-year age group. In this series one of the highest age incidences (ten cases) occurred in the 6-year-old group. That there is a true peak at this period, probably due to the tendency of medulloblastomas to occur at this age, is demonstrated by the histogram in Fig. 1, in which the age at time of admission to hospital is plotted against frequency. The data is taken from the reported series of brain tumors in children of Bailey and associates,[1] Marburg,[7] Smith and Fincher,[13] and the present series.

An analysis of the anatomic location of the tumors in this series confirms the findings of previous writers, namely, that tumors in children occur predominantly beneath the tentorium.[1, 3, 7, 13]

This work was done while the authors were in the Division of Neurological Surgery, the University of Chicago.

*From the Division of Neurological Surgery, The Johns Hopkins Hospital, Baltimore, Md.

TABLE I.

Hemispheral tumors	19
Third ventricle tumors	20
Cerebellar tumors	45
Tumors of the pons	12
Tumors of the base	4

TABLE II.

Gliomas	78
Meningiomas	5
Epithelial tumors	7
Sarcomas	8
Cysts, congenital	1
Angiomas	1

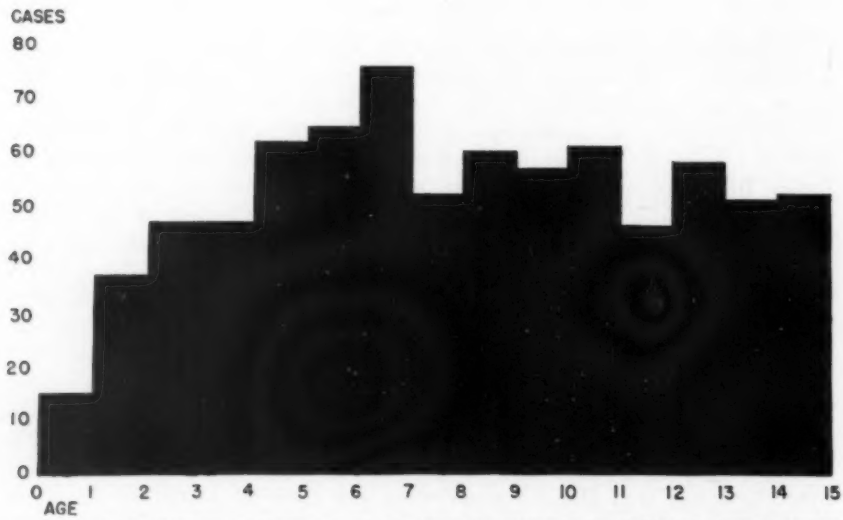


Fig. 1.—Histogram of frequency of intracranial neoplasms in childhood plotted against age. The data were collected from the series of Bailey and associates,[1] Marburg,[7] Smith and Fincher,[13] and the authors' cases.

The analysis of the tumors on a pathologic basis only emphasizes the fact that gliomas are proportionally more common in children than in adults.

A further breakdown on a combined anatomic and pathologic basis is of value only in indicating the predilection of certain tumors for specific anatomic locations.

Cerebellar Tumors		45
Astrocytoma	15	
Medulloblastoma	25	
Ependymal tumor	4	
Glioblastoma	1	
Tumors of the Base		4
Sarcoma	3	
Meningioma	1	

Third Ventricle Tumors			20
Pinealoma		1	
Epidermoid		1	
Glioma		11	
Craniopharyngioma		5	
Sarcoma		1	
Cavum vergae tumor		1	
Hemispheral Tumors			19
Glioma		9	
Glioblastoma	3		
Ependymal tumor	2		
Astrocytoma	2		
Oligodendroglioma	1		
Papilloma	1		
Meningioma		4	
Sarcoma		4	
Epithelial cyst		1	
Angioma		1	

This breakdown emphasizes the differences between tumors of childhood and adult life. Not only is there a marked predilection for tumors to occur in the posterior fossa, but certain of the tumors of adult life are entirely lacking in childhood. No example of an acoustic neuroma or pituitary adenoma is found in this series, although these tumors constitute almost 25 per cent of the neoplasms of adult life. The meningiomas are only about one-third as common in childhood as in adult life. On the other hand, tumors along the neural axis (medulla, pons, third ventricle) are much more common in childhood than adult life. Moreover, certain of the types of tumor encountered in these regions in adults, such as benign cysts, are rarely seen in children. These peculiarities of brain tumors in childhood have been emphasized by many previous writers.[1, 3, 7, 13]

GENERAL SYMPTOMATOLOGY

In general, brain tumors in children produce symptoms by reason of intracranial hypertension rather than by their local effect. Minor focal manifestations are likely to be ignored by children. Because of the great compensatory powers of the immature brain, a tumor is often asymptomatic until large enough to produce intracranial hypertension. The majority of neoplasms in childhood are located along the neural axis and early occlude the egress of ventricular fluid, causing an internal hydrocephalus. For these reasons the symptoms of increased intracranial pressure, vomiting and headache, are the most common early manifestations of brain tumors in children.

Vomiting.—The vomiting associated with brain tumors may have no distinguishing characteristics from that due to gastrointestinal disease. Frequently it is not accompanied by nausea and after a violent emesis the patient may sit down and eat a second hearty meal. But at times nausea is intense and persistent. The forceful "projectile" vomiting ascribed to brain tumors is the exception rather than the rule.

It is a curious fact that the vomiting is often precipitated by an illness or a head injury,[8] perhaps due to the increase of intracranial pressure produced by these conditions. Once begun, the vomiting may stop suddenly for weeks to

start again with or without provocation. Such capriciousness makes the diagnosis of tumor so difficult. Yet with the recognition that vomiting may be the first sign of an intracranial tumor, it is less frequent now that surgeons explore the abdomen for a lesion which lies in the head. But even the neurologist at times finds it difficult to make a positive diagnosis of the cause of so-called "cyclic or functional" vomiting.

Headache.—The headache due to brain tumors in children is not specific. It is often referred to the frontal region. Occipital and suboccipital discomfort is not uncommonly complained of, probably due to distention of the dura mater about the foramen magnum.

Children are usually unable to give a good description of their headache, so that the symptom rarely has reliable localizing significance. Perhaps the most characteristic feature is its occurrence early in the morning. Frequently it wakes the patient or begins on awakening. More often than not it is associated with vomiting, which, strangely, seems to relieve the headache. Aggravation of the headache by stooping, straining at stool, or coughing is rarely noted by children.

Staggering Gait.—The third most common manifestation of a brain tumor in a child is an unsteady gait, unquestionably a corollary of the fact that the neoplasms in this age group are predominantly subtentorial. The difficulty in walking has an insidious onset and is often attributed to weakness resulting from vomiting. But it is more than that. Occasionally it is the prime manifestation of the tumor and at times becomes so severe that the patient cannot stand unassisted.

Convulsions.—Epileptic manifestations are rarely associated with infratentorial tumors[15] but frequently occur with tumors of the cerebral hemispheres. The convulsions differ in no way from those in idiopathic epilepsy, for focal seizures commonly associated with brain tumors also are present in cryptogenic fits. Petit mal attacks, although not unknown, are rarely encountered in brain tumors of children. The majority of the seizures are generalized and may or may not have localizing phenomena. A true Jacksonian march is not common, but convulsions with focal beginnings such as jerking of the face, arm, or leg, are often encountered. Because idiopathic epilepsy is so common in children, such seizures are diagnosed as cryptogenic until the patient develops other neurologic manifestations such as papilledema, paralysis, etc. Occasionally "cerebellar fits" are confused with true convulsions. These attacks of rigid opisthotonus with or without respiratory and cardiac embarrassment are occasionally seen in patients harboring posterior fossa tumors. Only if a detailed account of the attack can be obtained is the differentiation from a grand mal attack possible.

Enlargement of the Head.—In infants and young children whose cranial sutures are not firmly united, enlargement of the head is often the first indication of a brain tumor. The resultant sutural diastasis in many instances may be palpated, or, if slight, recognized by the "cracked-pot" sound produced by percussing the parietal region. Roentgenograms of the skull are particularly

helpful in detecting this phenomenon. In infants the enlargement of the head may lead to the suspicion of a communicating hydrocephalus. Some cases have been so diagnosed only to have a tumor disclosed at necropsy. Subdural hematomas also cause cranial enlargement, but in many cases the head has a peculiar square appearance in contrast to the oval shape of the hydrocephalic head.

Weakness.—A paresis of an extremity, side of the face, or eyelids occasionally is the first sign of a neoplasm. The weakness is usually of extreme value in localization of the neoplasm, especially if generalized intracranial pressure is not present.

Diplopia.—A crossing of the eyes, usually an internal strabismus due to a unilateral or bilateral external rectus weakness, is a common complaint of children with brain tumors. The condition is usually due to tension upon the abducens nerve, and, associated with generalized intracranial pressure, is of no localizing value. Only if the diplopia occurs before intracranial hypertension has developed or if it is associated with other ocular abnormalities such as paresis of conjugate deviation, is it of localizing significance.

Other Symptoms.—Many other complaints are presented by children with brain tumors. Some are the result of intracranial pressure, such as drowsiness; others are due to focal brain involvement and may be of localizing value.

DIAGNOSTIC PROCEDURES

In children it is particularly important to utilize all available diagnostic techniques, for the clinical findings are so often few, nebulous, and sometimes misleading.

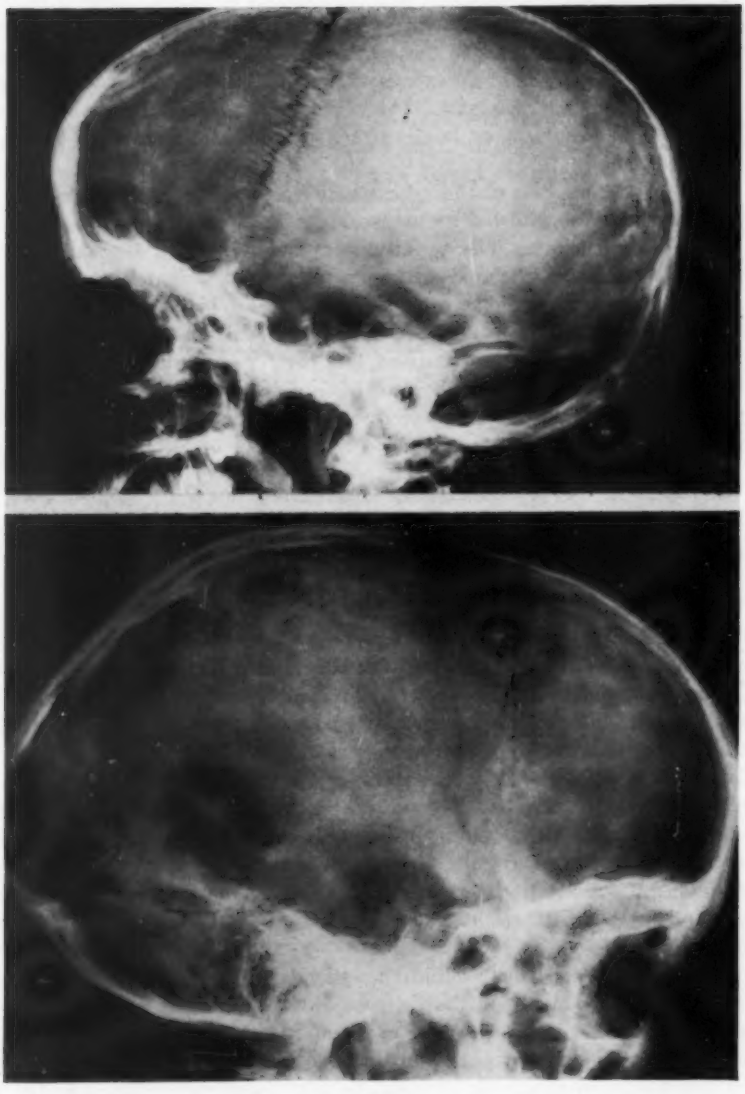
Roentgenograms of the Skull.—The routine raying of the skull in anteroposterior and lateral stereoscopic views is a basic necessity in all patients suspected of a brain tumor. Diastasis of the sutures, intracranial calcification, calvarial distortion, or erosion may give a clue to the location of the tumor. Special views of the optic foramen should be taken routinely unless the site of the tumor is obvious on clinical grounds. If the wrist is included on one of the skull views, the epiphysis may be examined for a lead line.

Electroencephalography.—The routine examination of the brain waves often is of localizing value and should be made in all cases. In tumors of the posterior fossa the electroencephalogram may not be of great significance, but occasionally the findings are positive.[12] Its greatest value is in the localization of hemispheral tumors and in the elimination of certain cases of idiopathic epilepsy as tumor suspects.

Angiography.—In young children suffering from posterior fossa lesions arteriography is a difficult diagnostic procedure because the vertebral artery is so small and inaccessible. In older children it is possible to puncture percutaneously the common carotid artery and occasionally the vertebral artery. When possible, angiography is of great help in determining not only the location but frequently the type of tumor.

Ventriculography and Pneumoencephalography.—In the absence of clinical evidence of intracranial hypertension, pneumoencephalography is a safe and valuable procedure. It may eliminate the likelihood of a brain tumor or it may

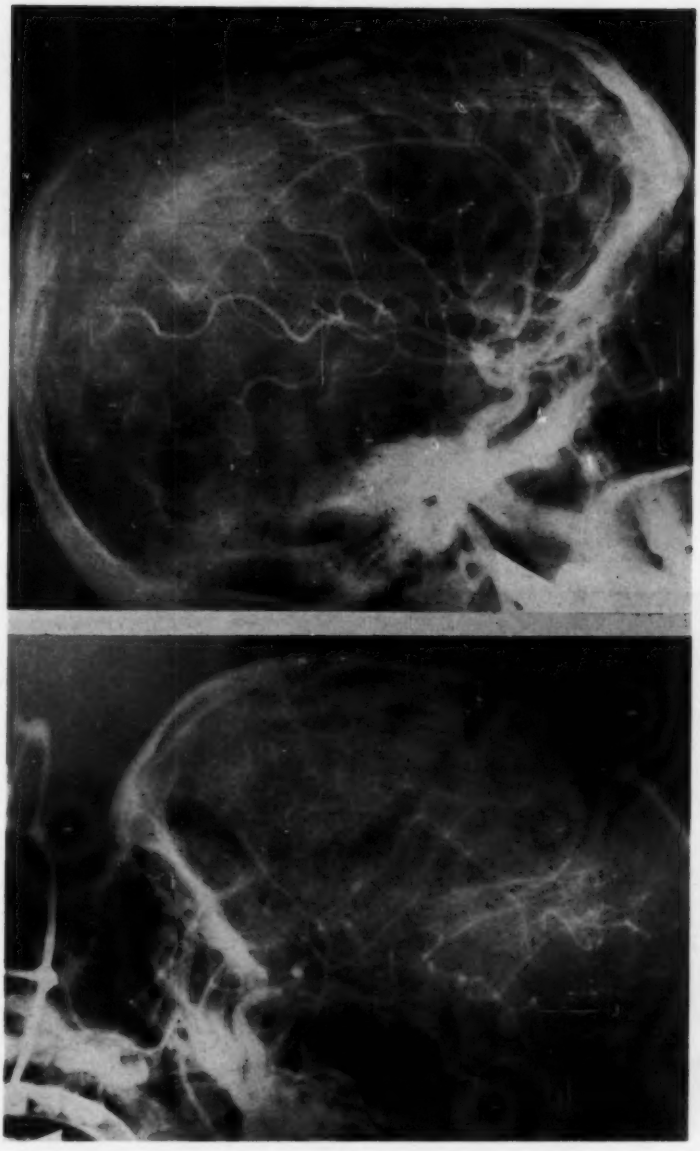
A.



B.

Fig. 2.—*A*, Lateral roentgenogram of the skull with slight sutural diastasis and convolutional markings due to intracranial hypertension. *B*, Lateral roentgenogram of the skull showing intrasellar and suprasellar calcification in a craniopharyngioma.

A.



B.

Fig. 3.—*A*, Lateral angiogram (arterial phase) to show the marked widening of the curve of the anterior cerebral artery due to internal hydrocephalus resulting from a congenital atresia of the aqueduct of Sylvius. *B*, Lateral angiogram showing the distortion of the carotid siphon due to a craniopharyngioma.

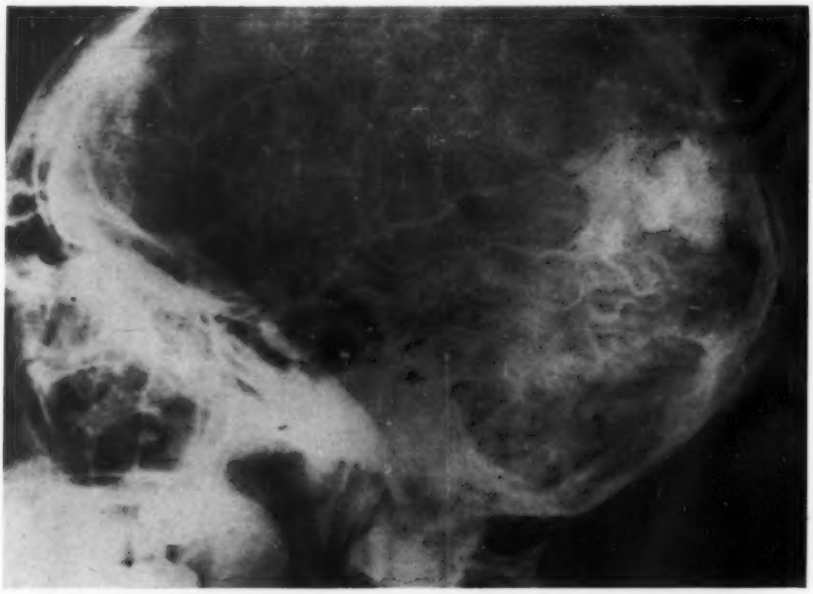


Fig. 4.—Lateral angiogram of a large posterior parietal angioma (retouched).

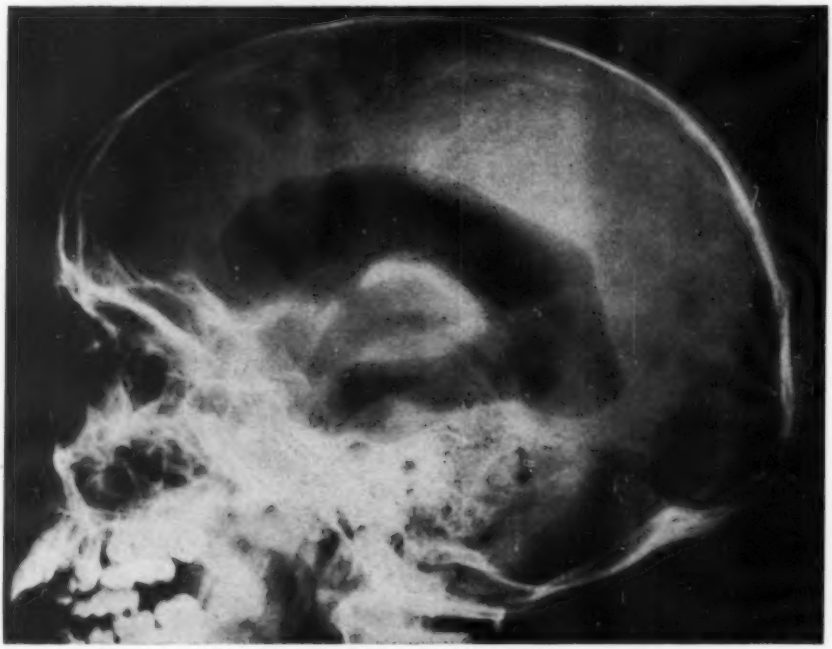


Fig. 5.—Lateral ventriculogram showing the posterior displacement and distortion of the fourth ventricle due to a pontine glioma.

enable a reliable diagnosis to be made. With increased experience and more accurate interpretation, the localization of tumors in the posterior fossa has been much improved.[4-6, 11] The value of air studies in localization of tumors of the cerebral hemispheres is well known. If intracranial hypertension is present, ventriculography is preferable to pneumoencephalography but carries a very definite risk. Many children harboring brain tumors react badly to ventriculography, so that an immediate surgical attack upon the tumor is necessary as soon as the air studies are completed.

Lumbar Puncture.—Lumbar puncture has no place in the diagnostic armamentarium when papilledema is present unless a burr hole has been made previously so that the ventricle can be tapped. In the absence of evidence of intracranial hypertension an examination of the spinal fluid will help in the differential diagnosis. But it must be emphasized that there is no spinal fluid finding characteristic of brain tumor.

Radioisotopes.—When radioactive tracers became available it was natural that attempts should be made to utilize them for localization of brain tumors. After demonstrating that fluorescein was concentrated within cerebral neoplasms, Moore and associates[9, 10] added radioactive iodine to produce diiodofluorescein. The location of the gamma radiation of this compound was then determined by counters applied to the head. Analysis of the amount of radiation enabled a correct localizing diagnosis to be made in most of the cases.

Another radioactive isotope, P32, has been used for localization of brain tumors.[2, 14] Because the radiation is a 1.69 Mev. beta ray with low penetration, this isotope, concentrated in the tumor, can only be detected when the counter is within 5 to 6 mm. of the neoplastic tissue. This has the advantage that a more accurate localization can be made with it than with radioactive diiodofluorescein, but only after the skull has been opened. To date these techniques have not been used extensively in brain tumors in children.

PRINCIPLES OF PATHOLOGIC ANATOMY AND PHYSIOLOGY ASSOCIATED WITH INTRACRANIAL TUMORS

A tumor within the intracranial cavity increases the intracranial contents by reason of its mass and, if it obstructs the ventricular system, by the resulting internal hydrocephalus. Often both the tumor and the increased ventricular fluid are responsible for augmenting the intracranial mass. Because the brain, cerebrospinal fluid, and tumor are practically incompressible and the skull is a rigid case, the growth of an intracranial tumor must be compensated for by enlargement of the cavity or by extracranial displacement of one of the normal intracranial constituents. In infants separation of the cranial sutures allows for enlargement of the head, but in older children the sutures are too firmly united to permit this mechanism to operate. Three main factors compensate.

1. *Decrease in the Amount of Spinal and Ventricular Fluid.*—There are normally approximately 150 c.c. of fluid within and about the brain and spinal cord. Two-thirds of this surrounds the spinal cord so that there are approximately 50 c.c. within the ventricular system, the cisterns, and subarachnoid spaces over the brain. This fluid occupies the various cisterns at the base of the

brain, the spaces about the sheaths of the cranial nerves, and the subarachnoid space over the hemispheres. It is this fluid which is the prime compensator for increased intracranial mass. This fluid is displaced by the moulding of the cerebral structures into the contour of the skull, first at the site of the tumor,

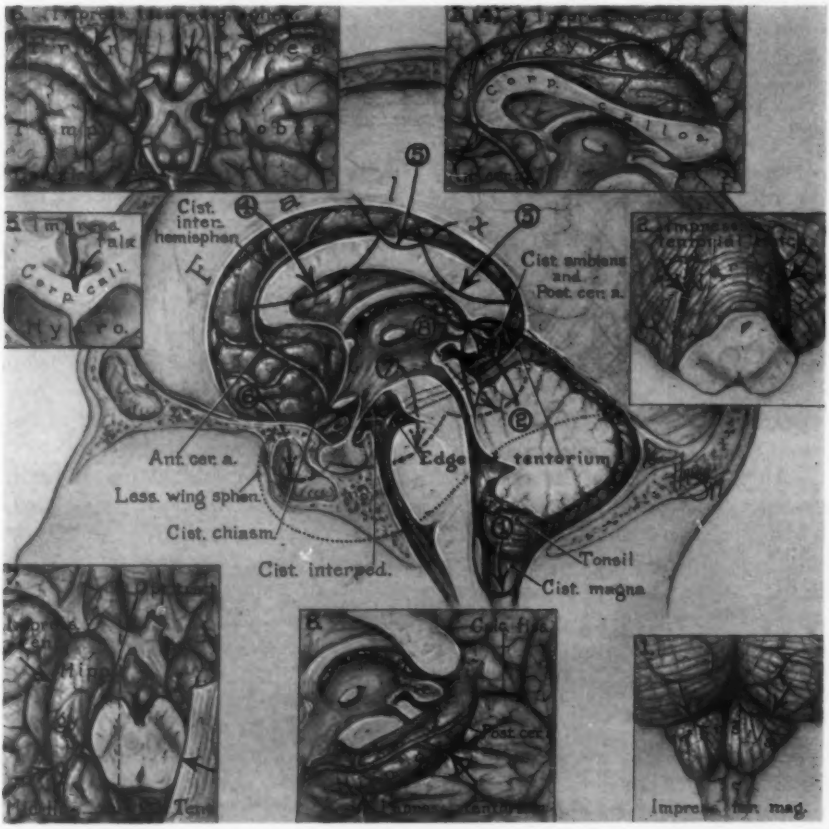


Fig. 6.—Diagrammatic representation of the distortion of the brain resulting from the growth of variously located intracranial neoplasms. The central sketch is a midsaggital section of the brain upon which are superimposed arrows indicating the direction of force exerted by the enlarging tumor. The number accompanying each arrow refers to the insert which illustrates the distortion produced by the particular force.

1, Displacement of the cerebellar tonsils through the foramen magnum, causing the well-known cerebellar pressure cone.

2, Displacement of the anterior lobe of the vermis cerebelli through the tentorial notch due to a posterior fossa tumor.

3 and *4*, Displacement of the gyrus cingulum under the tentorium by a parietal or frontal lobe tumor, producing an impression on the cortex of the falx.

5, Elevation of the corpus callosum, often due to an internal hydrocephalus, producing a notching of the superior aspect of the corpus callosum.

6, Displacement of the frontal lobe into the middle cranial fossa and pituitary fossa, usually the result of a frontal lobe tumor. The spenoidal wing produces an impression on the base of the frontal lobe and the margin of the sella turcica causes a groove across the gyri recti.

7, Displacement of the hippocampus through the tentorial notch with compression of the opposite cerebral peduncle and a groove at the site of the tentorial impression. This is frequently associated with temporal lobe tumors.

8, A slightly more posterior displacement than that in insert 7, often seen with occipital lobe tumors.

later at more distant points. Thus, with a frontal tumor, the frontal lobes are impressed upon the frontal bones, cribriform plate, the tuberculum sellae turcicae and optic nerves, and finally over the edge of the sphenoidal ridge. This process displaces the spinal fluid in the sulci of the frontal lobe, the fluid of the chiasmatic cisterns, and about the pituitary stalk. As a result of this moulding impressions are then seen on the orbital cortex about the olfactory stalks, about the olfactory trigone where herniation occurs into the pituitary fossa over the sharp posterior margin of the tuberculum sellae turcicae, and along the orbital cortex abutting the sylvian fissure. At the same time the frontal horns of the ventricle are compressed, thus decreasing the ventricular fluid.

In the presence of a temporal lobe tumor, the subarachnoid spaces over the temporal lobe are narrowed or obliterated, the sylvian fissure is compressed and pushed upward over the sphenoidal ridge, the pituitary cisterns are displaced, and the subarachnoid space about the brain stem is occluded by the medial margin of the hippocampus, which herniates about the incisura of the tentorium. This causes impressions below the sylvian fissure at the sphenoidal ridge and along the hippocampus. Simultaneously the temporal horn is reduced to a mere slit and the lateral ventricle may be compressed.

In the presence of a parietal lobe tumor, the subarachnoid spaces are narrowed, the ventricles compressed, and the inferior margin of the callosal gyrus often forced under the falx to the other side, thus compressing the subarachnoid space over the corpus callosum. This causes a groove along the callosal gyrus.

In the presence of an occipital lobe tumor the occipital subarachnoid space is compressed, the posterior part of the ventricular system narrowed sometimes to a slit, and the cisterna ambiens obliterated by herniating cortex of the precuneus into the space over the quadrigeminal bodies and about the lateral margin of the mesencephalon. This causes a groove along the precuneus and hippocampal gyrus due to the sharp edge of the tentorium.

In the presence of a posterior fossa tumor the brain stem and cerebellum are moulded into the orifices of exit of the cranial nerves, the foramen magnum, into which the cerebellar tonsils usually herniate, and into the cisterna ambiens, prepontine cistern, and the subarachnoid space about the mesencephalon. This moulding produces the well-known cerebellar pressure cone and a groove about the anterior lobule of the cerebellum due to the pressure against the incisura. The fourth ventricle is compressed and usually distorted.

These are the mechanisms by which the moulding of the brain decreases the amount of spinal and ventricular fluid. At first the changes may be local but as the pressure increases all of the above factors may be operating.

2. *Decrease in the Amount of Interstitial Fluid Within the Brain.*—Local compression of the brain causes a decrease in the size of the cerebral tissue, probably largely due to loss of interstitial tissue. Obviously the neuronal and neuroglial tissue cannot be eliminated, so that any compression must be the result of decrease in fluids. While some of this may come from the cell, most is probably from the interstitial spaces. That such compression does occur can be demonstrated readily by ventriculograms before and after elimination of a

block causing hydrocephalus. A markedly dilated ventricle before operation may decrease in size to an almost normal sized ventricle within a few weeks after the removal of an obstruction. This decrease in interstitial fluid is probably of extreme importance, for elimination of the cerebral spinal fluid about the brain maximally can only give 40 to 50 c.c. of additional space. Many brain tumors weigh several hundred grams, and dilated cerebral ventricles often contain several hundred cubic centimeters of fluid. The greater part of the space must have come from loss of interstitial fluids.

3. *Decrease in the Amount of Intracranial Blood.*—The importance of this factor is difficult to assess. That it does play a role is evident from the dilated, tortuous scalp views frequently seen in cases of brain tumor. The diploic channels are utilized to decrease the amount of blood in the cerebral views and longitudinal sinus. The arteries are also constricted, as may be seen in arteriograms of hydrocephalus.

This moulding and distortion of the brain as the result of the mass of a brain tumor often produces secondary alterations in the vascular and ventricular fluid systems. The most important of these concerns the changes about the mesencephalon as the result of incisural herniations. Not only may the uncal and hippocampal herniation cause mesencephalic compression, but it may produce narrowing of the aqueduct of Sylvius, resulting in an internal hydrocephalus. Thus the common ventriculographic picture of a temporal lobe tumor is compression of the ipsilateral ventricle and dilatation of the third and contralateral ventricles. This internal hydrocephalus markedly increases the intracranial tension, so that pressure symptoms may rapidly develop.

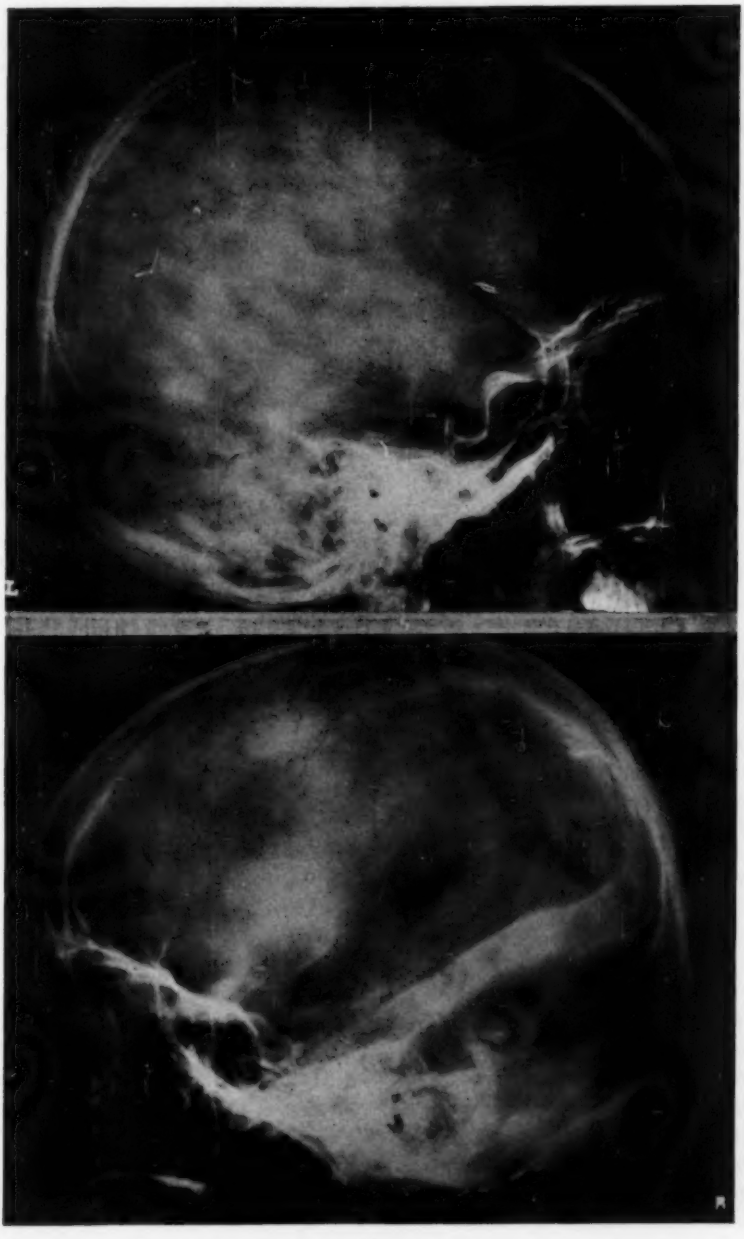
The effect of the tonsillar herniation about the medulla oblongata into the foramen magnum is well known. The effects of the other herniations are not so well recognized. Yet probably herniation through the tentorium is as common with supratentorial lesions as medullary compression by tonsillar herniation with infratentorial tumors. Moreover, uncal herniation may cause compression and thrombosis of the posterior cerebral artery as it passes about the brainstem to enter the calcarine fissure.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a brain tumor may be divided into two categories, one its differentiation from other diseases and the second its correct anatomic and pathologic designation. The first of these problems is a serious one but one which can be solved correctly in approximately 90 per cent of cases if certain criteria are kept in mind. The conditions which may be confused with a cerebral neoplasm may be classified under the following four headings:

1. *Congenital Abnormalities.*—Anomalies of the nervous system giving rise to hydrocephalus may simulate tumor, for often a congenital condition does not cause symptoms until some years after birth. The diagnosis of communicating hydrocephalus may be established by dye tests. Congenital atresias of the foramens of Luschka and Magendie give rise to a characteristic high location of the lateral sinuses which is readily recognized in roentgenograms of the skull.

A.



B.

Fig. 7.—Lateral roentgenograms of the skull showing: *A*, the high position of the lateral sinus and *B*, the enormously enlarged posterior fossa due to a congenital atresia of the foramina of Luschka and Magendie.

Megaloencephaly may occasionally cause a large head but rarely evidences of intracranial hypertension. Congenital atresia of the aqueduct of Sylvius, although rarely producing symptoms in infancy, may not be differentiated from a cerebellar or third ventricle tumor without the aid of air studies.

2. *Inflammatory or Toxic Conditions.*—Chronic infections of the meninges or brain often cause intracranial hypertension and sometimes focal neurological manifestations. The acute infectious meningitides rarely cause diagnostic difficulty due to the evidences of fever and malaise, but the more chronic meningitides, tuberculous, syphilitic, torula, etc., may occasion some confusion. These conditions are particularly likely to simulate third ventricle tumors. Chronic inflammatory tissue about the medulla may be responsible for an internal hydrocephalus.

Air studies, as well as a spinal fluid examination, may be necessary to eliminate the possibilitiy of one of these chronic infections of the meninges. Serous meningitis, associated at times with middle ear disease, may produce symptoms of a midline cerebellar tumor, but fortunately the condition rarely occurs. An examination of the spinal fluid for a virus may give a positive result, but in most cases a virus cannot be isolated.

Encephalitides may closely resemble a brain tumor. Usually the acute and rather diffuse signs and symptoms of the epidemic, Japanese B, St. Louis, and western equine encephalitis suggest the correct diagnosis. But parasitic infestations such as cystocerosis, echinococcic or hydatid cysts, and schistosomiasis may give rise to localized granulomatous masses. In countries where such conditions are endemic, the possibility of cerebral infection must be considered. Tuberculomas are also common in some lands (England and Chile), where they may constitute as much as one-third of all brain tumors; in this country they are extremely rare, being less than 1 per cent of brain tumors. A purulent encephalitis (brain abscess) may develop without febrile or toxic episode, especially if the primary infection has been treated with penicillin or sulfonamides. Signs of a focal expanding lesion may be the first evidence of its presence.

Of the toxic agents which may cause a clinical picture resembling that of neoplasm, lead is the most important. Roentgenograms of one of the long bones may show deposition of lead at the epiphysis, but this examination may be negative. A chemical determination of the lead level in the blood is the most reliable test.

3. *Vascular Disturbances.*—The severe vascular disturbances seen in adult life are rarely encountered in children, so that the differential diagnosis between vascular disease and neoplasm is not so important. Occasionally a patient with unrecognized kidney disease will be admitted as a brain tumor suspect, but examination of the blood constituents will suggest the correct diagnosis. Vascular anomalies such as angiomas may give signs of an expanding lesion of the brain. Usually, however, the onset is sudden and regression begins after the initial insult. The presence of a cutaneous nevus or a calcified "worm" intracranially may suggest the diagnosis.

4. *Traumatic Lesions.*—Subdural hematomas in infants are a common cause of enlargement of the head and convulsions. The diagnosis should be made

easily by a fontanel puncture. In children subdural bleeding is not so common as in adults but one of the authors has encountered a hematoma when doing an intended ventriculography for what was thought to be a brain tumor.

The differential diagnosis of one type of cerebral tumor from another is sometimes much more difficult. In this series several mistakes in localization have been made. Within the posterior fossa it may be difficult, if not impossible, to differentiate a pontine glioma from a cerebellar tumor, even with the aid of air studies.

A 2-year-old boy complaining of vomiting and unsteady gait was found to have normal optic discs, paresis of the third, fifth, ninth, and tenth cranial nerves on both sides and the sixth cranial nerve on the right side, hypotonia and ataxia of all extremities, an unsteady gait, and bilateral Babinski's signs. Because of the extensive cranial nerve involvement, the patient was thought to have a pontine glioma, but at autopsy a medulloblastoma of the cerebellar vermis was found.

A 9-year-old boy complaining of headache and vomiting for four months on examination was found to have nystagmus on looking to the right and left, paresis of the right sixth and seventh cranial nerves, generalized hypotonia, ataxia on the right side, and an unsteady gait. His fundi were normal. His fourth ventricle being well visualized in a ventriculogram, he was considered to have a pontine neoplasm; but on post-mortem examination a cystic cerebellar astrocytoma was found.

These two examples, the most outstanding in the series, must prove that it is impossible to make a consistently accurate pathologic diagnosis on clinical findings. On the basis of these cases it seems wise to explore and biopsy all suspect tumor cases of the posterior fossa.

It is even impossible at times to differentiate a supra- from an infratentorial tumor. A 6-year-old boy complaining of headache and vomiting for three months was found to have two diopters of papilledema, hypotonia, so much ataxia that he was unable to walk, and bilateral Babinski's signs. Preparatory to exploring the posterior fossa the surgeon, in tapping for the left posterior horn, encountered a cyst containing 50 to 60 c.c. of yellow fluid. Subsequently a glioblastoma was found to be in the left occipital and temporal lobes; the cerebellum was normal at autopsy a year later.

DISCUSSION

In most cases a child suffering from a brain tumor consults a physician because of a manifestation of intracranial hypertension such as headache, vomiting or papilledema, or excitatory or paralytic—focal dysfunction—of the brain. The diagnosis of neoplasm must be made on the course of the disease and other conditions which may simulate tumor must be eliminated. When a presumptive diagnosis of tumor has been made, its site and pathologic nature remain to be determined. In the absence of definite focal symptoms or findings, the tumor is likely to be located within the posterior fossa. However, tumors of the third ventricle in children often produce no diencephalic manifestations

and cannot be distinguished clinically from tumors of the posterior fossa. Accordingly, the aid of laboratory tests is essential in making a correct diagnosis in such cases. Roentgenograms of the skull may indicate the locus of a tumor by bony erosion or by calification. Arteriography is of great assistance without much risk. Air studies are often essential but usually must be followed by an immediate attack upon the tumor. Otherwise, vascular changes within the brain secondary to the altered hydrodynamics may precipitate serious signs of impending disaster. Radioactive isotopes may aid in the localization of the tumor.

Even with every technical aid an accurate anatomical and pathologic diagnosis may not be possible. If there is a reasonable possibility of finding an operable tumor the patient is entitled to an exploration. In the case of posterior fossa and hemispheral tumors a direct exploration seems advisable, but in the case of third ventricle tumors the mortality is so high that palliative procedures are wise. In most cases it is impossible to differentiate tumors of the third ventricle from those of the posterior fossa. Since benign tumors of the third ventricle in children are practically unknown, it has been our policy to explore the posterior fossa in such cases and, if no tumor is found there, to make a Torkildsen ventriculostomy, later giving x-ray therapy. This has lowered the operative mortality of third ventricle tumors and insures that an operable tumor of the cerebellum has not been overlooked.

The high incidence of malignant tumors and tumors along the cerebral axis make the general prognosis of brain tumors in children rather gloomy. But the excellent results achieved in cerebellar astrocytomas and certain cerebral tumors admit of some justifiable optimism.

SUMMARY

1. A series of 100 brain tumors in children is analyzed. A marked predilection for tumors to occur in the posterior fossa is found, as well as a tendency for tumors to develop along the neural axis.

2. Many types of tumor commonly seen in adult life—pituitary adenomas, meningiomas, acoustic neuromas—are rarely if at all seen in childhood.

3. The symptomatology of brain tumors in children is largely due to intracranial hypertension, although occasionally focal manifestations are present.

4. The mass of the tumor within the intracranial cavity is compensated for by a decrease in the amount of cerebrospinal and ventricular fluid, in the amount of interstitial fluid, and in the amount of blood in the intracranial cavity. This is accomplished by a moulding of the brain to fill all nooks and crannies ordinarily occupied by cerebrospinal fluid. Herniation about the mesencephalon or medulla may cause serious depression of vital functions.

5. The differential diagnosis of brain tumors is discussed.

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ACUTE LYMPHOCYTIC CHORIOMENINGITIS

A Study of Twenty-One Cases

William Roy Green, M.D., Shreveport, La., Lewis K. Sweet, M.D., Washington, D. C., and Robert W. Prichard, M.D., Boston, Mass.

SINCE the entity of lymphocytic choriomeningitis was separated from Wallgren's classification of acute aseptic meningitis[1] by the work of Armstrong and Lillie,[2] and of Scott and Rivers,[3] there have been about 150 supposed cases of the disease reported in the literature. In reviewing the published reports of these cases, it was found that many of them were presented with the etiological diagnosis having been poorly substantiated. This may have been due to the great difficulty attendant upon all virus studies. Since the diagnosis of this disease can be made finally only by virologic study, it is felt that these incompletely substantiated reports may have led to confusion and inaccuracy in the description of the natural history of the disease in man. In order to define more clearly the clinical picture produced by the disease, we are reporting our experience with twenty-one proved cases of acute lymphocytic choriomeningitis.

These patients were studied on the Communicable Disease Service of the Gallinger Municipal Hospital between July 1, 1938, and June 30, 1948. They include all patients for whom the diagnosis was conclusively established in this ten-year period.

The virus of lymphocytic choriomeningitis has been reported to produce three types of clinical illness in man.[4] These include grippal or systemic illness without central nervous system involvement, an acute meningitis, and an encephalitis. The milder, grippal, illness has been proved only in laboratory experiments and in workers handling the virus,[5, 6] and has been established in the general population only by the demonstration of animal protecting antibodies in a considerable number of adults whose history indicated no illness suggestive of meningitis.[7] No patient with this type of illness has been diagnosed in this hospital in the acute phase, nor have we had any patients in whom the encephalitic form of the disease has been diagnosed with certainty. Our experience includes twenty-one patients in whom an absolute diagnosis of the viral etiology of meningitis has been made. Our discussion will be limited to this one type of illness with which we have had experience.

CLINICAL MANIFESTATIONS

The first patient with this form of the disease was seen at this hospital in 1935 and the case has been reported elsewhere.[8] Since he was not seen by any of us, he is not included in this report.

The clinical findings in the twenty-one patients included in this study are summarized in Table I. The ages of these twenty-one patients ranged from 6 to 39 years. Four patients were in their first decade, six in their second, three in their third, and eight in their fourth. The distribution according to sex was fourteen females and seven males, a definite preponderance of females which

From the Department of Pediatrics and Communicable Diseases, Gallinger Municipal Hospital, Washington, D. C.

TABLE I. CLINICAL FEATURES OF TWENTY-ONE PATIENTS WITH LYMPHOCYTIC CHORIOMENINGITIS

				SYMPTOMS							FINDINGS					
CASE	SEX	RACE	AGE	ONSET	ANTECEDENT	MALAISE	ANOREXIA	HEADACHE	NAUSEA VOMITING	STIFF NECK	SENSORIUM	STIFF NECK	KERNIG BRUDZINSKI	TEMPERATURE MAX. ° F.	TEMPERATURE DUR. DA.	MISCELLANEOUS SYMPTOMS AND FINDINGS
1	M	W	38	Sudden	Grippe	+	+	+	+	0	Semicoma	2+	+	103	8	Cough
2	F	N	14	Insid.*	None	+	+	+	+	+	Semicoma	2+	+	104	10	
3	M	W	31	Insid.	Grippe	+	+	+	+	+	Cloudy	2+	+	101	4	Vertigo, tremor
4	F	W	21	Insid.	Grippe	+	+	+	+	+	Semicoma	2+	+	103	4	Cough, chest pain
5	F	N	17	Insid.	Grippe	+	+	+	0	+	Semicoma	2+	+	104	6	
6	M	N	30	Sudden	None	+	+	+	+	+	Cloudy	2+	+	102	3	Photophobia
7	F	N	23	Sudden	None	+	+	+	+	0	Clear	2+	+	102	5	Photophobia
8	F	W	15	Sudden	None	+	+	+	+	0	Clear	2+	0	102	6	Insomnia, nervous
9	F	N	6	Sudden	None	+	+	+	+	0	Clear	1+	+	104	5	
10	F	W	17	Insid.	None	+	+	+	+	0	Semicoma	2+	0	102	6	
11	F	W	33	Insid.	Grippe	+	+	+	+	+	Cloudy	2+	0	99	0	Photophobia
12	F	N	22	Insid.	Grippe	+	+	+	0	+	Clear	2+	+	102	3	Photophobia
13	F	N	18	Sudden	None	+	+	+	+	+	Cloudy	2+	+	102	3	Cough
14	M	N	17	Sudden	None	+	+	+	+	0	Comatose	2+	+	102	7	Photophobia
15	F	W	34	Sudden	None	+	+	+	0	+	Clear	2+	0	102	1	
16	F	N	39	Insid.	Grippe	+	+	+	0	0	Semicoma	2+	+	103	2	
17	M	N	9	Sudden	None	+	+	+	+	0	Cloudy	2+	0	101	4	Abdominal pain
18	M	N	6	Insid.	Grippe	+	+	+	+	+	Clear	3+	+	101	2	Photophobia, pneumonia
19	F	W	34	Insid.	Grippe	+	+	+	0	0	Cloudy	3+	+	102	4	Bilateral papilledema
20	M	W	32	Sudden	None	+	+	+	+	0	Cloudy	2+	+	102	3	
21	F	W	8	Insid.	Grippe	+	+	+	+	0	Semicoma	2+	+	105	5	Lobar pneumonia

*Insid. = Insidious.

has not been noted before. The four patients under ten years of age were divided equally between the sexes. The preponderance of adult female patients lends support to Armstrong's theory of the mouse reservoir of virus in the transmission of the disease[9] since adult females probably would have closer contact with mice and their excreta in the home than would males. The racial distribution was eleven Negroes and ten whites which corresponds fairly well with the racial distribution of patients seen in this section of the hospital.

The disease apparently occurs with greatest frequency in the spring and fall of the year, and is definitely less common in the summer. The distribution by months and seasons is as follows:

Jan.	Feb.	Mar.	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
1	1	2	2	3	1	0	1	1	2	5	2

Spring (March, April, May)	7	(4 females, 3 males)
Summer (June, July, August)	2	(1 female, 1 male)
Fall (September, October, November)	8	(6 females, 2 males)
Winter (December, January, February)	4	(3 females, 1 male)

The patients came from many social and economic levels, and from varied types of dwellings, from hovels to middle-class suburban homes. Three of our patients were found to have mice infected with the virus of lymphocytic choriomeningitis in their dwellings, and have been reported by Armstrong and Sweet,[10] and Armstrong, Wallace, and Ross.[9] Three of our patients came from dwellings on the same street, two in one block separated by one house, and one in the next block. In the apartment of one of these three patients mice infected with the virus were trapped. All three of these patients yielded the virus from their spinal fluid.

Headache was the most common single complaint, and was present in all instances. There was no particular localization, though it was frequently described as being generalized, with some accentuation "behind the eyes." Its intensity is marked. Headache persisted for an average of 12.6 days, the longest being thirty days (two cases), and the shortest three days. This symptom frequently was relieved entirely, though temporarily, by lumbar puncture.

Nausea and vomiting were present on or before admission in sixteen of the twenty-one patients, and in three instances continued after admission to the hospital. It is possible that the decrease in intracranial pressure resulting from the lumbar puncture may have relieved the cause of this symptom in most of the patients.

Photophobia was present in six patients, and persisted after admission for several days. It was not related to the fever, occurring when the patient was afebrile. Funduscopy was normal in these patients. The only patient in the series with papilledema did not complain of photophobia.

Under grippal symptoms, we have grouped nonspecific symptoms such as sore throat, malaise, generalized aches and pains, and anorexia. All of our patients complained of feeling bad, and anorexia usually was present at one time or another during the course of the disease. Ten of our patients had definite symptoms of grippe at the onset of their illnesses. Eight of these were treated as such for five or more days before the headache and other complaints

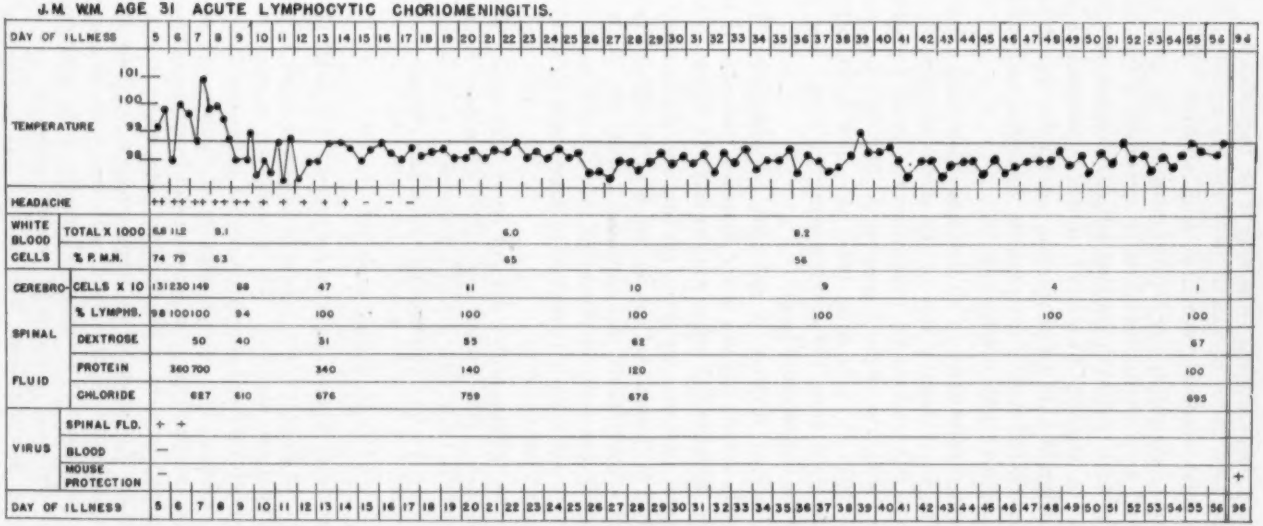

Chart 1.—J.M. (Case 3) became ill five days before entry with headache, fever, vomiting, and pains in the joints and back. His illness became progressively worse until his admission to the hospital. The patient lived in a mouse-infested home from which nine mice were trapped five days before the onset of his illness. Examination revealed an alert cooperative man who was acutely ill and was complaining of headache. He had a stiff neck, positive Kernig's and Brudzinski's signs and hyperactive tendon reflexes. His pain was reduced by lumbar puncture, though it recurred and persisted for eight days. He was asymptomatic during the remainder of his stay, but remained in bed because of abnormal spinal fluid findings. The diagnosis of lymphocytic choriomeningitis was confirmed by direct isolation of the virus from the spinal fluid, and by the development of virus-neutralizing antibodies in the blood.

became so severe that hospitalization was sought or recommended. Four of these ten patients had been ill for periods of from one to six months with vague complaints, such as mild headache, weakness, and lassitude. They had been diagnosed as "nervous exhaustion," or "psychoneurosis" by their physicians. Each of the four had an accentuation of their symptoms a few days before admission. Eleven of our patients presented an onset typical of that seen in purulent meningitis. A clear-cut history of sudden appearance of meningeal symptoms, which progressed until hospitalization was sought, was obtained from these patients. About 50 per cent of our patients, therefore, had grippal symptoms before the onset of meningitic involvement.

Fever was present on admission in all patients except one, whose temperature was 99° F. The fever usually was of the sustained variety (Chart 1), disappearing by lysis. The maximum temperature is given for each patient in Table I. During the course of the disease in the hospital the temperatures varied from 100 to 105° F., averaging 102.3° F. The fever persisted for periods of from one to ten days, the average being 4.4 days. The pulse rate was in keeping with the temperature level.

All patients presented stiffness of the neck on admission. The nuchal rigidity was moderately severe, usually being classed as two plus or three plus. The Kernig's and the Brudzinski's signs were positive in sixteen patients.

Of our twenty-one patients, six were rational on admission; the others ranged from "cloudy" to "comatose," in the words of the admitting examiner. One had experienced a convulsion. All appeared acutely ill. Since the word "benign" unfortunately has been incorporated into the nomenclature of this disease, we feel that it is particularly important to stress the severity of the illness that may be seen among these patients.

There were several findings which did not occur with sufficient frequency to be mentioned separately. One patient complained of urinary retention which persisted from the sixth to the eighth day of her illness. Other complaints, each in a single instance, were syncope, vertigo, abdominal pain, tremor, and insomnia.

LABORATORY FINDINGS

The laboratory findings on these patients are presented in Table II.

The *spinal fluid* findings on the specimen obtained from initial lumbar puncture in each patient are recorded. The patients are arranged in order of descending cerebrospinal fluid cell counts. Lumbar punctures were performed as indicated after admission, but only the significant findings will be discussed here. Specimens of spinal fluid were collected in sterile rubber-stoppered tubes, refrigerated immediately, and sent to the National Institute of Health, Bethesda, Md., as soon as possible for attempts at virus isolation. All spinal fluid cell counts were done immediately on the ward, with and without acetic acid for the removal of erythrocytes. Differential cell counts were performed on the stained smear of the sediment obtained by centrifugation of a portion of the spinal fluid. Dextrose determinations were carried out by two methods. In some instances the five-tube method of Alexander,[11] which provides a roughly

quantitative estimation of the sugar level, was done immediately on the ward. The central laboratory performed the standard Folin-Wu[12] type of quantitative determination on freshly drawn fluid.

TABLE II. LABORATORY FINDINGS IN TWENTY-ONE PATIENTS WITH LYMPHOCYTIC CHORIOMENINGITIS

			CEREBROSPINAL FLUID					BLOOD			
CASE	DAYS ILL	TEMPERATURE (TIME OF TAP)	TOTAL CELLS	LYMPHOCYTES (%)	PROTEIN	SUGAR	VIRUS	INCREASE IN SERUM ANTIBODY	TOTAL WHITE BLOOD CELLS	POLYMORPHONUCLEARS (%)	LYMPHOCYTES (%)
1	15	102	3,370	95	405	<10*	+	+	9,000	74	25
2	7	104	2,500	99	Pandy 4+	37	+	−(37 days)	5,800	74	24
3	5	100	2,300	98	360	N†	+	+	6,750	NR‡	NR‡
4	4	104	2,090	97	NR‡	<10*	+	+	7,650	74	24
5	7	104	1,550	98	90	N†	+	NR‡	5,600	NR	NR
6	3	102	1,500	90	211	N†	+	NR	6,400	70	28
7	5	102	1,350	100	210	40	+	+	8,500	60	29
8	5	102	1,300	100	Pandy −	50	+	+	4,800	50	46
9	4	104	1,300	100	NR	N†	+	NR	10,750	42	47
10	8	102	1,200	90	237	N†	+	NR	8,500	NR	NR
11	7	99	1,200	90	49	20	+	NR	8,350	38	58
12	10	103	1,100	90	260	N†	+	+	7,320	60	40
13	3	102	840	90	88	79	+	NR	5,900	NR	NR
14	4	102	710	95	112	29	−	+	5,400	NR	NR
15	10	102	592	100	85	60	−	+	6,200	80	20
16	14	103	530	100	113	40	+	NR	10,500	NR	NR
17	2	101	427	90	50	50	−	+	4,100	14	83
18	7	101	330	95	58	N†	−	+	12,850	54	44
19	30	102	225	95	131	30	−	+	9,800	NR	NR
20	2	102	210	90	140	50	+	+	12,000	64	24
21	2	105	142	100	NR	<10*	−	+	25,800	84	14

* By qualitative test.
†Normal by qualitative test.
‡NR = No record.

The admission cell count appeared unrelated to the degree of temperature and fell to normal long after the temperature had reached normal limits. The total count on admission varied from 142 cells to 3,370 cells, the average being 1,179 cells. The most striking finding in connection with the cell count was the observation that a high cell count increased the likelihood of isolating a virus from that specimen. Of the fifteen fluids which yielded the virus, only three had cell counts below 1,000, containing 840, 530, and 210 cells, respectively. Also, fluids obtained earlier in the disease are more likely to be virus-containing than later specimens. Eleven of our virus-containing fluids were obtained in the first week of their disease, the remaining four being collected on the eighth, tenth, fourteenth, and fifteenth day of illness, at which time they had high cell counts, 1,200, 1,100, 530, and 3,370, respectively. This finding suggests that the virus may be attached to the cells, and that study of the centrifuged sediment for virus might yield a higher number of positives than the use of all the cerebrospinal fluid.

The name of the disease indicates the usual finding in the differential cell count. The spinal fluid from all our patients contained from 90 to 100 per cent lymphocytes, none lower.

The spinal fluid dextrose at initial and subsequent examinations was normal on all specimens from fourteen patients. Seven patients presented one or more readings with decreased dextrose content (30 mg. per cent or less). Five patients, Cases 4, 11, 14, 19, 21 showed a definite decrease in the initial spinal fluid dextrose as noted in Table II, but were found to have normal spinal fluid dextrose at subsequent examinations. In two patients, extremely interesting decreases in the level of this substance were noted. In one patient (Case 1) the admission spinal fluid contained 3,370 cells, and by qualitative test there was no reduction of Benedict's solution in any of the five tubes indicating a dextrose content of 10 mg. per cent or less. On the following day there was again no dextrose by qualitative test, the cell count being 1,625 at that time. Two days later the cell count was 699, and the dextrose was normal, remaining so on the two following examinations at five- to seven-day intervals. Another patient (Case 13) on admission showed 840 cells, dextrose 79 mg. per cent; four days later her cell count had risen to 2,300 and there was no dextrose by the qualitative test. The following day the absence of dextrose was again demonstrated with a cell count of 1,460. Two days later her cell count was 1,890, her spinal fluid dextrose 50 mg. per cent, her blood sugar 94 mg. per cent. On the two following taps, with cell counts of 340 and 21, normal spinal fluid dextrose was found. Both of these patients (Cases 1 and 13) had the virus isolated from their spinal fluids.

In ten instances out of the sixteen in which protein determinations were done on the initial spinal fluid specimen, the protein value was above 100 mg. per cent. In twelve patients this value was exceeded sometime during the course of the disease. Values ranged from 20 to 700 mg. per cent, and it is worth noting that late in the disease, after the cell count had returned to normal, some patients were found to have a protein level above 100 mg. per cent. Had the latter cases been seen for the first time at this stage, a question might well have been raised as to the cause of such albuminocytologic dissociation. One consequence of the increased protein seen in this disease is the formation of a pellicle, a phenomenon which is evidently still regarded by some practitioners as a sign of tuberculous meningitis. It is hoped that this venerable fear of the really nonspecific pellicle will eventually be dispelled.

In two of our patients the fluid from which the virus was isolated also gave a doubtful, and a weakly positive, reaction, respectively, to a serologic test for syphilis. The specimens giving these reactions also showed a first zone colloidal gold curve of the type commonly called "paretic." Succeeding examinations in both patients revealed normal reactions, the examination being repeated twice again in each case. In the first patient, blood serologies ranged from two plus to four plus, and a competent syphilologist who examined the patient opined that hers might well be a case of a positive reaction due to nonsyphilitic disease. She did not return for the suggested follow-up examinations, and her exact status with regard to syphilis is unknown. The second patient had negative blood serology. These findings suggest that it is possible to obtain a positive reaction to the usual laboratory serological test for syphilis from the spinal fluid of patients with lymphocytic choriomeningitis.

The determination of spinal fluid chlorides was performed only sporadically in our patients, since we feel that little is to be learned from this test on the cerebrospinal fluid. The chloride content of the spinal fluid seems to bear a direct relation to the chloride level in the blood, and it is lowered by any condition affecting the blood chloride level, such as the vomiting and excessive sweating seen in many diseases, especially the meningitides.

The blood picture in fifteen of our twenty-one patients was normal, the white count varied from 4,800 to 10,000, with a normal differential count. Two patients had pneumonia; one had a white blood count of 25,800, the other a count of 12,850 with the usual polymorphonuclear response. Two patients had cervical adenopathy and white blood counts slightly elevated. One 9-year-old boy had a white count of 4,100 with an increase of lymphocytes.

The erythrocyte sedimentation rate was performed on only four of our patients, and all were normal. Farmer and Janeway[13] raised the interesting point that the sedimentation rate in lymphocytic choriomeningitis is normal, whereas that in tuberculous meningitis is not. We have not had sufficient experience to make any statement on the subject, but feel that further observation is indicated.

Except for traces of albumin during their febrile period, the urines of most of our patients showed nothing remarkable or specific.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The exact diagnosis of lymphocytic choriomeningitis is based on the isolation of the virus from the spinal fluid of patients in the acute stage of the disease, and/or demonstration of an increase in the titer of antibody against the virus following the acute illness in question. Our patients all fulfilled these criteria, fifteen yielding the virus, the remainder showing a definite rise in neutralizing antibody titer. In reviewing the literature on this disease, it was noted that many cases have been presented in which the diagnosis of lymphocytic choriomeningitis was made solely on clinical grounds; usually this diagnosis was appended if no evidence for tuberculosis or syphilis was discovered and the patient recovered. In several reports,[14-16] however, patients diagnosed clinically, without virus isolation, died, and the autopsy findings were presented as those of fatal lymphocytic choriomeningitis.[14, 15] We feel that reporting of this nature will only confuse the clinical or pathological picture of the disease. We feel that definite demonstration of an etiological agent must be accomplished before it is possible to assign an etiological diagnosis to a disease which varies so slightly from certain other diseases.

The differential diagnosis of lymphocytic choriomeningitis is complicated by the fact that there are a host of conditions that may produce a serous meningitis which is quite similar in clinical manifestations to that caused by the virus of lymphocytic choriomeningitis. Even in the best circumstances the specific diagnoses of those that are due to agents other than syphilis or tuberculosis usually are made with difficulty, if at all. To aid in the differentiation the following outline, with some examples of each, is suggested:

I. *Viral*
- A. Primary infection of the central nervous system
  1. Lymphocytic choriomeningitis
  2. Poliomyelitis
  3. Encephalitis (various forms)
- B. Secondary infection (associated with rubeola, epidemic parotitis, varicella, rubella, vaccinia, etc.)
- C. Viruses that may invade the central nervous system (herpes simplex, infectious mononucleosis, lymphopathia venerum)

II. *Bacterial*
- A. Tuberculosis
- B. Infection with *Hemophilus influenzae* (rarely)

III. *Spirochetal*
- A. Syphilis
- B. Weil's disease

IV. *Irritative*
- A. Chronic inflammation impinging on the meninges

V. *Chemical*
- A. Lead poisoning

VI. *Fungus*
- A. Torula

VII. *Protozoa*
- A. Toxoplasmosis

VIII. *Unknown etiology*
- A. Serous meningitis in scarlet fever

In the group of diseases due to viruses, if the season for poliomyelitis is in progress or in view, this disease must be kept in mind until proof of some other etiology is available. Even if a patient is admitted without evidence of the type of paralysis that is characteristic of poliomyelitis he should be examined *daily* for evidence of muscular weakness. Usually the total cell count in the spinal fluid is lower, and the differential count usually shows not over 70 per cent lymphocytes. In some patients, however, there may be over 90 per cent lymphocytes. The shift from polymorphonuclear cells to lymphocytes, as seen frequently in poliomyelitis, has never been observed in lymphocytic choriomeningitis. The various forms of encephalitis are diagnosed specifically only by virologic study, and present a widely overlapping clinical picture, with signs of diffuse involvement of the central nervous system. The history must be meticulously taken on the subject of exposure to contagious disease. Thus a patient who has no clinical evidence of mumps may have a mumps meningoencephalitis, the etiology of which might go unappreciated if a history of exposure were not obtained. The mumps skin test,[17] and finally, mumps complement fixation antibody determination will establish the diagnosis firmly. In general, serous meningitis associated with the exanthemata and vaccinia is accompanied by a lower cell count than most of the cases of lymphocytic choriomeningitis and is diagnosed by the other manifestations of the disease. Virus infections other than those commonly associated with exanthemata may be present in the central nervous system; for example, infection with the virus of lymphopathia venereum.[18] The virus of herpes simplex, which is widespread in the human

system, rarely invades the central nervous system, and may cause an illness clinically indistinguishable from lymphocytic choriomeningitis. (See below.) As yet unknown is the cause of the central nervous system involvement seen in infectious mononucleosis, where presumptive evidence strongly points to a virus as the etiological agent. The blood picture and the Paul-Bunnell test are of aid here.

Rarely one sees a purulent meningitis that in its early stages may assume a serous form; that is, the pleocytosis in the spinal fluid is predominantly lymphocytic. We have seen *Hemophilus influenzae* meningitis appear in this fashion on several occasions, the diagnosis being made by identification of the organism on smears or cultures of the cerebral spinal fluid.

The differentiation of tuberculous meningitis from lymphocytic choriomeningitis may be extremely difficult. As a rule, the cerebrospinal fluid dextrose is lowered in tuberculosis, but this finding may come late in the disease, and as shown above even relatively persistent reduction of cerebrospinal fluid sugar does not eliminate the possibility of lymphocytic choriomeningitis. The protein and chloride content of the spinal fluid are of little differential value. The total cell count usually is less in tuberculosis, and the differential count usually shows a smaller proportion of lymphocytes. However, the total cell count in tuberculous meningitis frequently numbers well over 200, and the differential count may show over 90 per cent lymphocytes. The definite differentiation of these two conditions can be made most satisfactorily by the demonstration, in patients with tuberculous meningitis, of tubercle bacilli in the spinal fluid, or of tuberculosis elsewhere in the body. Since tuberculous meningitis frequently is a manifestation of hematogenous tuberculosis, the examination of the bone marrow by the technique of Katz, Lifschutz, Milloff, Geiger, and Marshall[19] has proved to be extremely useful in establishing the diagnosis of tuberculous meningitis.

Spirochetal infections usually are diagnosed readily. Serological evidence of syphilis together with a suggestive history will permit diagnosis. Weil's disease is accompanied by icterus which may result in xanthochromia of the spinal fluid. Agglutination reactions are essential in the diagnosis of this disease.

Mastoid disease and brain abscess may produce serous meningitis by irritation of the contiguous meninges, and are revealed by physical examination and localizing neurological signs.

Lead poisoning may produce a chemical meningitis. Typical blood changes and abnormalities in x-rays of the long bones showing a deposition of lead at the growing ends lead to a correct diagnosis. Intrathecal medication, especially with therapeutic sera, will produce a meningeal reaction, as will iodized oil or air which is allowed to enter the cerebrospinal system.

The meningitides due to fungi are poorly understood, with the exception of that due to *Cryptococcus hominis*. Occasionally the cryptococcus may resemble a lymphocyte, and if any suspicion concerning morphology of the cells arises, further test, such as the India ink test, should be done. The investigation of obscure meningitides with cultural methods aimed at fungus isolation is to be recommended if our knowledge of these diseases is to be broadened.

Toxoplasmosis affecting the central nervous system is most frequently seen in infants and is characterized by convulsions and a picture suggestive of encephalitis or hydrocephalus. The spinal fluid may contain from 20 to 2,000 cells. X-ray evidence of calcification inside the skull, with demonstration of agglutinating and complement-fixing antibodies against the toxoplasma organism aid in diagnosis. Examination of the fundi is often of great help in these cases. Serous meningitis[20] has been seen in approximately one per cent of patients with scarlet fever at this hospital, the cause being unknown. The meningitis is indicated by the recrudescence of fever after the disease seems to be abating, accompanied by signs of meningeal irritation that often are minimal. It is not related to purulent complications of the disease. The spinal fluid findings are almost identical with those of choriomeningitis, though in general the total cell count is somewhat lower.

After all of the above conditions have been weighed, the etiology is still obscure in a majority of cases; it is for this reason that we do not assign, for recording purposes, the diagnosis of lymphocytic choriomeningitis except when the diagnosis has been established conclusively. Perhaps there are still those who feel that clinical acumen is sufficient to make the diagnosis of lymphocytic choriomeningitis; and indeed, the temptation is strong. We present the following brief abstract for consideration in this regard. This patient, who was seen in this hospital, has been previously reported by Armstrong.[21]

A 15-year-old Negro boy was admitted to the hospital in December complaining of a "cold" for one week, nausea, vomiting and severe headache for twenty-four hours, and semistupor for the twelve hours preceding admission. His only previous hospitalization had been for a "concussion" following an auto accident a year before. Physical examination showed an acutely ill, semistuporous Negro boy with a temperature of 101.4° F., pulse 100, blood pressure 140/70. Three plus nuchal rigidity and positive Kernig's and Brudzinski's signs were present and were the only positive findings on physical examination. Spinal fluid examination at this time revealed 900 cells, 96 per cent lymphocytes on stained smear, protein 120 mg. per cent, normal sugar, chlorides, Kahn, and colloidal gold curve; there was no growth on culture in the fluid. A repeat spinal tap was done ten days later, a specimen of the first fluid having been sent to Dr. Armstrong for virus isolation. In the interim the patient's meningeal signs had disappeared by the third day, and his temperature had become normal the fourth day. The second specimen showed 69 cells, 90 per cent lymphocytes, 80 mg. per cent of protein, other normal values. For the next week he remained afebrile, and was discharged after a third lumbar puncture showed 19 cells, all lymphocytes, a protein of 260 mg. per cent, and other normal values. It was felt throughout this boy's illness that he was suffering from lymphocytic meningitis, most probably lymphocytic choriomeningitis caused by the virus of Armstrong and his co-workers. He was signed out as acute lymphocytic meningitis, etiology undetermined.

Final identification of the virus recovered from his spinal fluid showed it to be the virus of herpes simplex.

We have had other patients, especially with mumps meningoencephalitis without parotitis, who have presented an almost identical problem in differential diagnosis.

CLINICAL COURSE AND MANAGEMENT

In nineteen of our twenty-one patients the course of the disease has been short, self-limited, and benign, in the sense that there were no residuals nor any deaths. The average hospital stay for this group of patients was twenty-seven days. The fates of the individual symptoms and signs have been previously discussed. Two of our patients pursued courses that were essentially the same as the others, but developed severe and prolonged headaches, with evidence, on readmission for these complaints, of increased intracranial pressure which required periodic spinal punctures for relief. One man was heard of three years after his initial hospitalization, still unable to work steadily because of his headaches. The second patient who developed this complication was known to have had headaches for several months. He was last heard of three years after his initial hospitalization, complaining of low back pain while in an Army camp; no mention was made of headache at that time. Since he had had a portion of a spinal puncture needle broken off in his paravertebral muscles, with subsequent surgical removal, the back pain cannot be assigned to lymphocytic choriomeningitis. The headaches probably were a result of the meningitis.

F. T. A. H. M. AGE 6 ACUTE LYMPHOCYTIC CHORIOMENINGITIS.

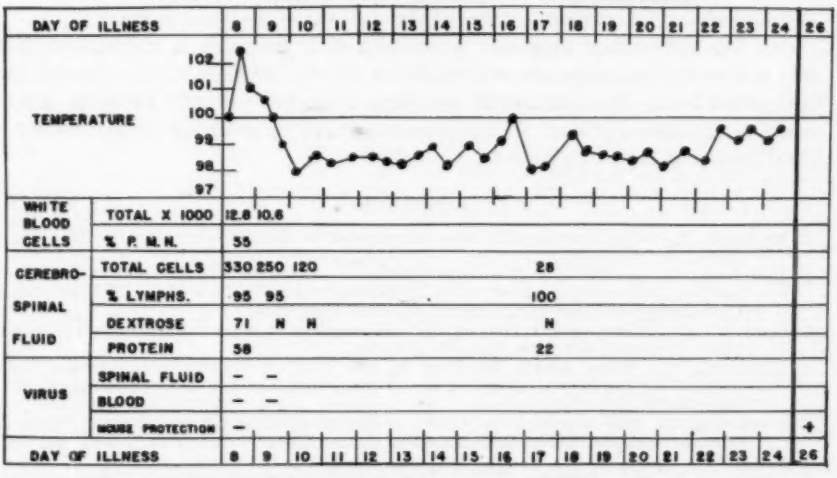

Chart 2.—F.T.A. (Case 18) became ill with headache, stiff neck, anorexia, photophobia, and intermittent fever and vomiting six months before his admission to the hospital. He had vomited with increasing severity during the week before admission. On examination he was a small, poorly developed, apathetic child who was not seriously ill. He showed classical signs of meningeal irritation. Within two days after admission he ceased vomiting and was greatly improved. The diagnosis of lymphocytic choriomeningitis was proved by the fact that he developed virus-neutralizing antibodies in his blood.

The prognosis as to life and aftereffects is excellent. We have seen no deaths in this disease, and complications only as noted.

The treatment of this disease is completely symptomatic, and consists of complete bed rest and analgesics, with fluid and diet control as indicated by the

patient's symptoms and general condition. The most important item is the complete bed rest. The two patients who developed headache, presented above, were among the first patients in our series. Both were allowed to get out of bed when their temperature fell and when they felt as though they would like to get up, at which time their pleocytosis had not subsided. The unfortunate outcome of their cases has led to the policy, perhaps based on coincidence, of keeping patients with meningitis on bed rest in the hospital until the cerebrospinal fluid has receded almost to normal, then to remain in bed at home for four to six weeks following discharge. Since this regime has been enforced we have not encountered any complications in these patients.

Prontosil was reported by Rosenthal, Wooley, and Bauer[22] to have a specific effect in inhibiting the production of lymphocytic choriomeningitis in mice when given with the infecting inoculum. Clinical trial of the drug showed that it was without effect in a small series. We have had no experience in its use.

Two patients had pneumonia complicating their disease. They were treated with sulfonamides and responded satisfactorily with no apparent difference from the usual course of such infections.

SUMMARY

1. Twenty-one patients with lymphocytic choriomeningitis are presented. The clinical and laboratory features of the disease are discussed in detail.

2. The differential diagnosis is outlined and the point is emphasized that only a presumptive diagnosis is possible on clinical grounds in this disease, the final proof being the isolation of the virus from the patient's blood or spinal fluid, or the demonstration of an increasing titer of antibody in the patient's blood following the acute illness.

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OBSERVATIONS ON THE TREATMENT OF A CASE OF GLYCOGEN STORAGE DISEASE

GEORGE H. LOWREY, M.D., AND JAMES L. WILSON, M.D.
ANN ARBOR, MICH.

THE treatment of the hepatic form of glycogen storage disease has been unsatisfactory since the establishment of that condition as an entity by von Gierke in 1929. Many methods of therapy have been attempted but few, if any, have resulted in benefit to the patient. We recently have had the opportunity to observe a boy with this disease over a fairly long period of time. Treatment while under our care has consisted of a high protein and low carbohydrate food intake. The symptomatic response of the child to these dietary measures was so satisfactory that we believe the results are worth reporting.

No attempt will be made to give a general review of the nature of the disease as this has been well done by others.[1-5] A summary of some of the important clinical factors for the purpose of orientation seems pertinent to the present discussion. Glycogen storage disease is a disorder of carbohydrate metabolism in which excessive deposition of glycogen occurs in certain tissues. Either because of abnormal stability of the glycogen, or more probably, because of some disturbance in the enzyme system concerned with its metabolism, this glycogen once deposited becomes extremely resistant to mobilization. Two distinct types of the disease have been described, one involving the liver and the other the heart. Coexistence of the two types is not known to occur. Other organs or organ systems may be involved, particularly excessive deposits may be found in skeletal muscle and kidney, but rarely to such a degree as to cause marked clinical symptoms.[1-3] Diagnosis of the hepatic type depends upon the following findings: hepatomegaly, rapid development of hypoglycemia and ketonuria when food is withheld, a subnormal or absent response of the blood sugar to injection of epinephrine, and the demonstration of abnormally large quantities of glycogen in the liver. Valuable confirmatory evidence may be obtained if it can be shown by in vitro studies that the liver glycogen is unusually stable.[3, 4] The glycogen content of the blood has been found to be elevated in all cases where such a determination has been carried out.[4, 5, 7] Lipemia may be present early in the disease.[2-4, 6] A bleeding tendency due to lowered prothrombin is often observed. Failure of growth and physical development are common. The condition probably begins in utero but may not be apparent until several months after birth when an enlarged liver is first noted. Episodes of hypoglycemia with weakness, vomiting, and convulsions may be the first symptoms that bring the attention of the parents to the abnormal condition.

The etiology of the condition remains obscure. Heredity plays a prominent role in a small percentage of cases.[3-5, 12] Humphreys and Kato[13] suggested that there is an abnormal persistence of fetal behavior of tissues. In support of this

From the Department of Pediatrics and Contagious Diseases, University Hospital.

contention they state that fetal and infantile tissues have a high glycogen content, and further, that carbohydrate mobilization from these established depots is poor in the young infant. The possibility that some endocrine dysfunction exists in these patients, as suggested by some investigators,[1, 17] is not well substantiated in the light of our present knowledge.

Crawford[5] was able to collect a total of fifty cases of the hepatic form of von Gierke's disease from the available literature to 1946. Others have reported a much larger number,[1, 13] but it is doubtful that all of these were true examples of this condition. Other diseases which may cause confusion in the differential diagnosis are extreme fatty infiltration of the liver,[14] galactosemia which is often associated with hepatomegaly,[15, 16] and cirrhosis of the liver. Any of these three conditions may cause hepatomegaly with signs or symptoms of hypoglycemia. A failure of response of the blood sugar to epinephrine injections like that found in von Gierke's disease may be present. However, a persistent ketonuria is not common to any of the three. The demonstration of galactosuria is confirmatory evidence of galactosemia. Finally, liver biopsy will prove the diagnosis if special studies are carried out to demonstrate the presence of abnormally large quantities of glycogen and the absence of fatty infiltration or cirrhotic changes. Other forms of hepatomegaly in children are usually easily differentiated.

REPORT OF A CASE

R. M. was first seen at the University Hospital, Jan. 12, 1948, at the age of 2 years and 2 months. His mother, a graduate nurse, gave a reliable history of the boy's progress up to that time.

He was the result of a full-time pregnancy and weighed 8 pounds at birth. It was noted that he had a large abdomen at birth but for some time thereafter this was thought to be due to the large amount of food ingested. He was breast fed for two months, but during this entire time a supplementary formula of evaporated milk with added carbohydrate was offered and taken. He was apparently well for the first three or four months of life. After this time it was first noted that if he "slept through" his night bottle he would experience mild, generalized, clonic convulsions early in the morning. They rarely lasted more than a minute or two and always stopped after formula was given. He frequently vomited a portion of his first morning feeding. No vomiting occurred later in the day. When the intervals between feedings were shortened neither of these symptoms appeared, with few exceptions, until the child was about 10 months of age. With the increased activity that the patient showed at this age the convulsions again became prominent, occasionally occurring as often as two to three times a day, but most severe in the early morning before the first feeding. At this time he was put on a high carbohydrate diet of three meals a day plus frequent feedings between meals and always a late night feeding. At the time the patient was admitted to this hospital an average day's consumption consisted of about 1,300 to 1,400 calories of which more than 60 per cent was carbohydrate and about 25 per cent was protein. On this regimen he would have periods as long as two months without convulsions. In addition to treatment by diet the boy had received short courses of thyroid and pitressin therapy but without demonstrable benefit.

The mother stated that the patient had always been mildly dyspneic and this was exaggerated on even slight exercise. He would often awake in the

morning covered with sweat and would be too weak to sit up. During this entire time there had been a gradual increase in the size of his abdomen. His development had been normal in every respect except as previously indicated. He had had few respiratory infections and no other illnesses.

The boy had been under the care of several physicians before being seen here. At 8 months of age a biopsy was obtained of the liver. Unfortunately, the exact glycogen content of the tissue was not obtained. However, Best's carmine stain revealed a marked increase in the glycogen content of nearly all cells. There were no cirrhotic changes present. The fat content, by histologic examination, was not considered abnormal.*

At one year of age he was admitted for studies in another hospital. At that time his weight was 23 pounds, his height was 29½ inches, and the liver was markedly enlarged. A glucose tolerance test using 25 Gm. of glucose by mouth was carried out with the results shown in Table I:

TABLE I

	BLOOD SUGAR
Fasting	48 mg. per cent
½ hour	97 mg. per cent
1½ hours	136 mg. per cent
2 hours	100 mg. per cent
2½ hours	63 mg. per cent
3 hours	44 mg. per cent

There was no appreciable response of the blood sugar to an injection of epinephrine at 15-, 30-, or 45-minute intervals. Following ingestion of 16 Gm. of galactose none was found in the urine within a three-hour period. After being on 32 mg. of desiccated thyroid for one month a repetition of the glucose tolerance test was carried out with results similar to the original test.†

The family history was essentially none contributory to the present illness. Both parents were living and well and one younger sibling was apparently normal. There was no evidence of a similar disease in either side of the family. Before becoming pregnant with the patient the mother had received thyroid and "injections of pituitary" for amenorrhea for a brief period.

Physical examination at this hospital on Jan. 12, 1948, revealed a child who appeared undernourished but not acutely ill. His height was 32 inches and his weight was 26.5 pounds. The most striking feature on general inspection was the great enlargement of the abdomen in an otherwise very slender body habitus. His respirations were somewhat labored, and this was increased by even very mild exertion. His gait and posture were normal for his age. His mentality seemed normal and he was cooperative and of a pleasant disposition. There was a generalized shotty lymphadenopathy involving the cervical, postauricular, and inguinal nodes. The veins were unusually prominent over the protuberant abdomen. The liver displaced the diaphragm about three finger-widths upward on the right as compared to the left. The border of the liver could be palpated from the left upper quadrant extending downward into the right iliac fossa. The edge was sharp, firm, smooth, and none tender. It was so large that palpation for other organs or masses in the abdominal cavity was

*We are indebted to Dr. E. Berkley Neal, of Roanoke, Va., for the report of the biopsied material.

†The results of these tests were kindly furnished us by Dr. P. J. Howard of the Pediatric Department of Henry Ford Hospital, Detroit.

unreliable. No fluid was demonstrable. The only other remarkable finding was that the anterior fontanelle was patent and admitted one finger. (He had received adequate vitamin D intake since very early infancy.)

Routine laboratory studies were as follows: hemoglobin 11.5 Gm., 3.6 million red blood cells, 13,200 white blood cells, a normal differential blood count, urinalysis was negative except for a strongly positive acetone test after a six-hour fasting period. The test for diacetic acid was negative on this same specimen.

The morning after admission the patient had fasted for eight hours. He was very irritable, sweating profusely, and appeared to the mother to be going into one of his mild convulsive seizures. At this time the patient was given 1.70 Gm. of gelatin per kilogram of body weight and within fifteen minutes he was quiet, comfortable, stopped sweating, and became cooperative. After ingestion of the gelatin he was fasted for four hours and the amino acid content of the blood was determined at frequent intervals during this time.[8] Within one-half hour there was a rise of more than 2 mg. per cent and this rise was sustained over the four-hour period. We interpret this test as showing an adequate absorption of protein from the gastrointestinal tract.

Because of the apparent relief in symptoms due to ingestion of protein, the following morning the same procedure was followed except that blood sugar determinations were made. Table II shows the results obtained.

TABLE II

TIME	BLOOD SUGAR (CAPILLARY)
Fasting	45.0 mg. per cent
½ hour	67.5 mg. per cent
2 hours	97.5 mg. per cent
4 hours	75.0 mg. per cent

Blood sugar determinations were then made on two subsequent days using two separate diets throughout each day. Both diets contained approximately 1,400 calories. On the first day, 60 per cent of the calories were in the form of carbohydrate and 15 per cent as protein. On the second day 40 per cent of the caloric intake was protein and about 30 per cent as carbohydrate. Fig. 1 shows the response of the patient's blood sugar to each diet.

We took advantage of the patient's presence to do certain other metabolic studies. These revealed a normal rate and level of absorption of an oily preparation of vitamin D taken orally; normal blood levels of calcium, phosphorus, phosphatase, and pyruvic and lactic acids; stool fat was 2 per cent by dry weight; total urine organic acid excretion in twenty-four hours was equivalent to 160 c.c. of 0.1 N hydrochloric acid (a value well above average ranges); acid-base studies on venous blood revealed the following values:

HCO_3	19.6 meq. per liter
Chloride	98.0 meq. per liter
Protein	18.4 meq. per liter
Total base	152.5 meq. per liter
pH	7.31

Roentgenograms of the chest were negative for many abnormalities of the heart, lungs, or thoracic cage. There was no marked retardation of skeletal maturation, as judged by the appearance of carpal centers.

Because a low carbohydrate and high protein diet resulted in less fluctuation of the blood sugar throughout the day and in less of a drop of the blood sugar after fasting for six to eight hours, the patient was discharged from the hospital on that type of a diet. This was calculated to average 1,400 calories daily and contained protein 140 Gm., fat 50 Gm. and carbohydrate 80 to 100 Gm.

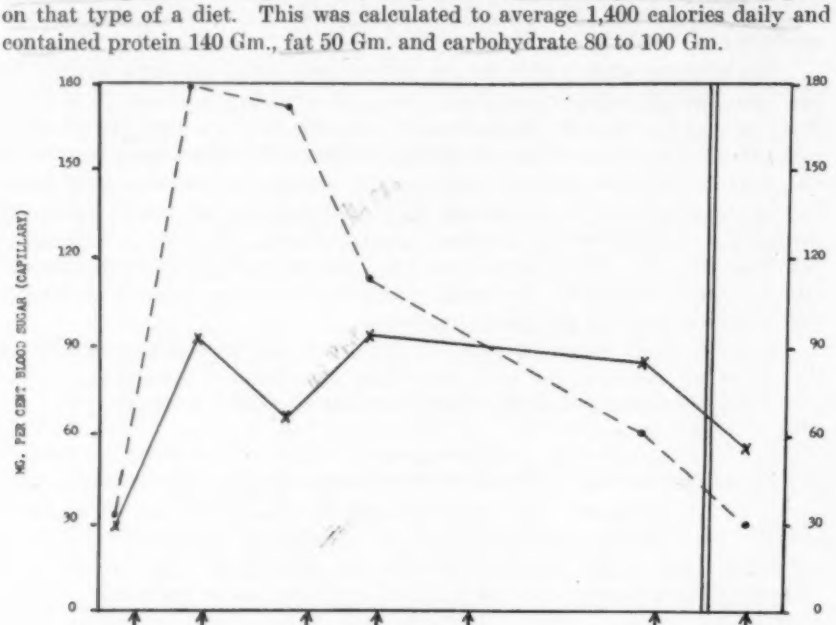

Fig. 1.—Response of the blood sugar level of a patient with glycogen storage disease to changes in diet. The broken line represents the levels obtained while on a high carbohydrate diet. The solid line represents the blood sugar levels obtained while on a high protein-low carbohydrate intake. The determinations were all made before the ingestion of food as indicated and extended over a twenty-four hour period.

The boy returned to this clinic for observation after a year on this regimen. His height was 34¾ inches (a gain of 2¾ inches in one year which is slightly less than normal for his age); his weight was 31 pounds (a satisfactory gain although the patient was still below normal weight for age). The abdomen was still very large, but the liver size was estimated to have remained stationary. The anterior fontanelle was closed. He was very cooperative, active, and mentally alert. There appeared to be less dyspnea with exertion than a year previously.

He had religiously adhered to the prescribed diet and his mother stated that at no time did she have difficulty in getting him to eat it. Both of his

parents were enthusiastic over his response to this treatment. He had had no convulsions during the entire year. This was in marked contrast to his previous history when the longest interval between convulsions was two or three months. He no longer had early morning sweats or weakness. He could now be dressed and eat his breakfast with the family rather than being fed immediately upon awakening in the morning. He could fast for as long as fifteen hours without symptoms. It was not necessary to give a late night interval feeding, although he continued to get this occasionally. He played more actively than formerly without undue tiredness or exhaustion. Except for a mild upper respiratory infection, he had been quite well.

Laboratory studies showed a hemoglobin value of 11.5 Gm. and a white blood count of 12,000. An early morning urine was entirely negative except for a strongly positive acetone test. The acetone disappeared during the day but was present again in another fasting specimen. Capillary blood sugar determinations were as follows: before breakfast 28 mg. per cent on one occasion and 46 mg. per cent on another, before lunch 81 mg. per cent, and before supper 68 mg. per cent. During these determinations his eating habits and diet were planned to correspond exactly to those in his home. Blood levels of calcium, phosphorus, phosphatase, electrolytes, and total protein were similar to those obtained when first observed.

The child has continued to progress as described up to the present time (aged 3½ years), and he has not experienced further convulsions over a period of nearly eighteen months. He has only three meals a day.

DISCUSSION

All attempts at the treatment of glycogen storage disease have been very disappointing. A very obvious reason for this was the absence of a sound knowledge of the pathogenesis of the disease. It is now generally recognized that the hepatic form of this condition is caused by an abnormality of the enzyme system which is essential for the mobilization of glycogen stored in the liver. It would appear from experimental evidence that the glycogen itself is not different from that found in the livers of normal subjects.[3-5]

A logical conclusion from these observations would be to supply the missing or abnormal enzymes necessary to liberate the glycogen depots. Such an approach was attempted by Bridge and Holt[4] who administered pancreatic extracts both orally and by injection to patients with von Gierke's disease. The results of this method of therapy were unsuccessful. No similar attempts have been made by others.

The various methods of treatment have been reviewed at some length by van Creveld.[1] Many endocrine preparations have been used including pituitary extracts,[1] thyroid,[1, 2] various fractions of the adrenal cortex,[1, 4] and epinephrine. None of these have resulted in any appreciable change in the disease when used alone or in various combinations. Other agents which have been tried include whole liver, liver extracts, choline, cholic acid, lecithin, and x-radiation. None of these have been of value in well-substantiated cases of glycogen storage disease.[1-4] Furthermore, there seems to be no logical rationale behind their use.

Bile salts were used by Matheson[17] in the treatment of a case. He reported "disappearance of ketonuria and decrease in girth of the abdomen" as the result of such therapy. However, even slightly prolonged periods of fasting caused reappearance of acetone in the urine, and there was no reduction in the palpable size of the liver after several months. Finally, the response of blood glucose to injections of epinephrine remained lower than normal in spite of treatment. This patient had never manifested any symptoms due to hypoglycemia. It is difficult to see how bile salts would influence the enzyme system in the liver.

Since it seems improbable to attack the fundamental defect in this condition at the present time, we are left with only symptomatic therapy. Aside from the very marked enlargement of the liver and the physical embarrassment caused by it, a major symptom results from the associated hypoglycemia. This was certainly true in our patient and in many others reported in the literature. Two factors apparently may lead to the production of symptoms in cases of hypoglycemia regardless of their cause. First, but not necessarily of primary importance, is the rapidity of the fall in blood sugar, and second, the relative carbohydrate starvation of tissues regardless of the blood level. It has been pointed out that the latter explanation may account for hypoglycemic reactions when blood sugar is at a normal level, or the absence of such reactions when this level is abnormally low.[9] Although the variations in the glucose content of the blood are important, the activity of the brain in controlling its own consumption of glucose appears to be of greater significance[9, 10] It may be postulated that a slow drop in the blood sugar for brief periods finds the brain and other tissues in a condition set to maintain themselves until the supply again becomes available.

Conn[11] suggested the use of a high protein diet in the treatment of hyperinsulinism. He was able to prove that such a measure resulted in a better sustained blood sugar level than any other diet, and that it resulted in more satisfactory symptomatic treatment than frequent feedings of carbohydrate. Such a diet, due to the relatively slow gluconeogenesis from protein, will supply a more constant source of glucose for the body. Bridge and Holt[4] suggested that a "protein meal" before bedtime for one of their patients with von Gierke's disease led to considerable improvement of the hypoglycemia. Later Bridge[2] mentioned a high protein intake as a part of therapy but continued to rely upon frequent feedings as a major portion of the therapeutic program.

It is possible that reducing the carbohydrate intake in a patient with glycogen storage disease will reduce the available sugar that can be converted and stored as liver glycogen. It must be admitted that such reasoning is purely hypothetical. If such treatment could be started very early in life, would the hepatomegaly be less pronounced?

The only treatment given to our patient was that of placing him upon a high protein and low carbohydrate diet. This resulted in very dramatic improvement of his symptoms which has continued up to the present time. Hypoglycemia and acetonuria are still in evidence and the degree of hepatomegaly has remained the same as before the special diet was begun. We are, therefore,

forced to conclude that the beneficial effect is due to the less rapid fluctuation and drop of the blood sugar levels when on a high protein-low carbohydrate intake. Laboratory evidence lends support to this contention.

SUMMARY

A typical case of the hepatic type of von Gierke's disease in a 2-year-old boy is reported. Symptoms associated with hypoglycemia were a prominent part of the condition. He was put on a high protein and low carbohydrate diet with very dramatic relief of these symptoms. Laboratory evidence supports the clinical impression that improvement was due to the more sustained blood sugar levels and less rapid fall to hypoglycemic values when placed on such a diet. It is probable that the fundamental disease process was little altered by such therapy.

We wish to express our appreciation to Miss Jean Fulkerson, head dietitian for the pediatric services, who aided us very greatly in calculating all of the diets and making valuable suggestions as to various foods to use in them.

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THE EFFECT OF PREOPERATIVE ROENTGEN-RAY THERAPY ON ARTERIAL HYPERTENSION IN EMBRYOMA (KIDNEY)

J. Edmund Bradley, M.D., and Miles E. Drake, Ph.D., M.D.
Baltimore, Md.

ROENTGEN-RAY irradiation of the adrenals[1] to reduce arterial hypertension has been reported and paradoxically the kidneys of dogs have been irradiated to produce experimental arterial hypertension.[2] The effect of preoperative roentgen-ray irradiation on hypertension in eleven cases of renal embryoma (Wilms' tumor) was reported by Daniel.[3] Briefly, the results obtained by this author were that in a total of five patients who had extreme arterial hypertension (125 mm. Hg or more), three had a marked reduction of the blood pressure within three weeks, one had no apparent change in blood pressure, and the remaining patient had a massive hemorrhage into the tumor with resultant shock and anemia, before the blood pressure could be determined. Six patients with normal or only moderate elevation of blood pressure (110 to 125 mm. Hg) demonstrated no alteration in blood pressure readings.

In the original description[4] of the association of hypertension with Wilms' tumor, we reported five cases in which hypertension was present. There was only one case in this series in which preoperative irradiation had been used, and in this case widespread metastases was exhibited to the skull and orbit, as well as to the liver; there was no effect upon the extremely elevated blood pressure. Since our original report there have been twelve cases of Wilms' tumor admitted to the University Hospital. Ten of these patients had hypertension. These ten patients were given preoperative roentgen-ray irradiation. As seen in Table I, blood pressure determinations were not made on patient No. 6, and in patient No. 5 there was no clinical evidence of hypertension. Four patients given preoperative irradiation had a marked fall in blood pressure five to eight days after the beginning of treatment. Three of these four patients had a detectable reduction in size of the tumor, but this was preceded in all cases by the change in blood pressure. Two of the patients (Nos. 7 and 9) in this treated group are still alive after five and one-half and eight years, respectively. The blood pressure of both are well within normal limits at the present time. Six patients given preoperative irradiation did not respond with any lowering of blood pressure or in the size of the tumor five to eight days after beginning treatment. One patient (No. 10) had no reduction in tumor size even though there was reduction in blood pressure. One patient (No. 8) had a normal blood pressure (Fig. 1) following preoperative irradiation, which persisted following nephrectomy and remained within normal range until six months later, when with the development of pulmonary metastases hypertension occurred. Irradiation to this area resulted in a return of the blood pressure to normal limits. There was no evidence clinically or by roentgenologic examination of recurrence of the tumor at the original site. However, upon her return four months later

From the Department of Pediatrics, University of Maryland School of Medicine, and University Hospital.

TABLE I

NO.	PATIENT	AGE	SEX	BLOOD PRESSURE ON ADMISSION	BLOOD PRESSURE BEGINNING OF THERAPY	TOTAL UNITS OF X-RAY	BLOOD PRESSURE END OF THERAPY	TUMOR RESPONSE TO X-RAY	OPERATION	BLOOD PRESSURE POST-OPERATIVE	BLOOD PRESSURE DISCHARGE	COMMENT	RESULT
1.	W. B.	18 mo.	M.	170/132	156/118	1530	172/118	No apparent change	Nephrectomy	—	—	Exitus on table	Died
2.	W. S.	5 yr.	M.	156/110	154/98	2214	136/80	No apparent change	Laparotomy	142/86	126·90	Inoperable tumor	Died
3.	J. B.	5 yr.	F.	140/110	120/90	2250	90/60	Mass reduced in size	Nephrectomy	106/76	102/78	2 mo. later widespread metastasis	Died
4.	M. L.	19 mo.	F.	110/98	114/92	2872	118/88	No apparent change	Laparotomy	114/90	122/90	Death one month later	Died
5.	M. E.	4 yr.	F.	100/70	—	—	—	—	Nephrectomy	102/68	98/70	Postoperative irradiation given	Still alive 8 mo.
6.	L. S.	3½ yr.	F.	?	?	2666	?	No apparent change	Laparotomy	?	?	Cachexia and death one month later	Died
7.	C. M.	17 mo.	M.	140/92	140/90	1936	110/66	Mass reduced in size	Nephrectomy	92/58	90/60	3 years later B.P. 92/58	Living after 5½ yr.
8.	E. B.	8 yr.	F.	168/124	150/110	2536	120/82	Mass reduced in size	Nephrectomy	120/80	110/74	Metastasis to liver and lungs	Died
9.	G. L.	2½ yr.	F.	170/110	144/104	1212	114/68	Mass reduced in size	Nephrectomy	104/60	100/60	Blood pressure normal	B.P. normal 8 yr. later
10.	N. B.	3½ yr.	F.	140/100	144/100	1261	104/78	No apparent change	Laparotomy	100/70	100/70	B.P. 6 weeks postoperative 140/110	Died
11.	M. H.	6 yr.	M.	160/122	158/118	1224	152/120	No apparent change	Laparotomy	156/116	—	Widespread metastasis to skull, liver, lungs, orbit	Died
12.	M. A.	1 yr.	F.	130/80	126/86	1670	130/76	No apparent change	Nephrectomy	130/84	126/94	Readmitted 5 mo. later B.P. 130/100. Pulmonary metastasis	Died

there was a large mass filling the entire right abdomen and there had been an increase in the pulmonary metastases. During this admission the patient suddenly one evening became speechless and developed temporary blindness and loss of hearing; shortly thereafter the patient had a generalized convulsive seizure. The blood pressure reading at this time was 220/160 mm. Hg. The convulsions were finally controlled after one hour with sodium luminal and magnesium sulfate. Death of this patient occurred eleven and one-half months following the initial admission. A post-mortem examination showed widespread pulmonary and hepatic metastases, but no evidence of tumor recurrence at the original site and with no involvement of the right kidney.

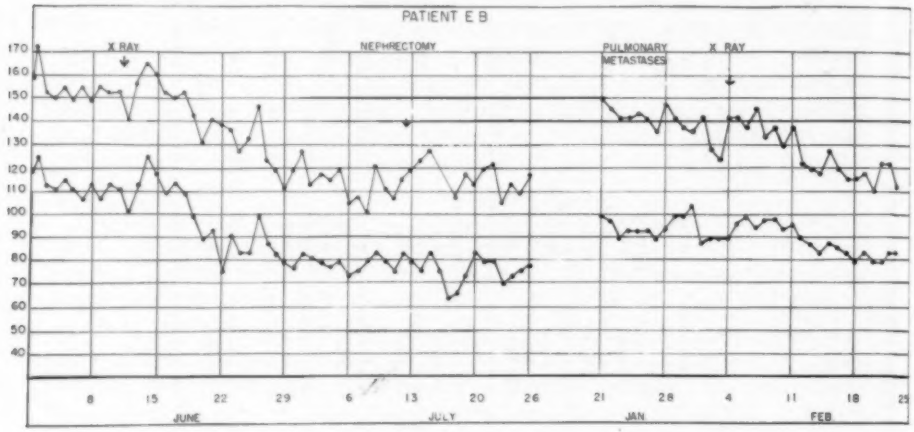

Fig. 1.

DISCUSSION

The cause of the hypertension seen in Wilms' tumor remains unknown. At the time of the original report of the occurrence of arterial hypertension with Wilms' tumor it seemed significant that[5] we were reporting a unilateral renal lesion with clinically manifest hypertension which seemed to confirm Goldblatt's experimental observations. Added significance seemed to be attached to our observation when Page[6] produced hypertension in the dog by wrapping one kidney in cellophane. The resultant appearance of the dog's kidney was not at all unlike the gross appearance of Wilms' tumor with the striking separation of encapsulated tumor from apparently normal renal tissue. However, as more and more cases of unilateral renal lesions with hypertension were reported, it became increasingly apparent that the experimental work of Goldblatt, Page, and others had but limited clinical application. So the advocates of hypertension of renal or a focal vasoconstrictor origin continue to be pressed by those who adhere to a neurogenic and a general vasospastic origin. The hypertension seen in Wilms' tumor does not offer any particular solution to the problem but presents rather new problems. While the preponderant majority of patients with renal

embryoma have an associated hypertension, some do not, as seen in patient No. 5. The variability of the hypertension is also of interest. Some have a very marked hypertension, others of only a moderate degree. Apparently the severity of the hypertension does not provide any prognostic index as in patient No. 9 where a 2½-year-old white girl had an admitting blood pressure reading of 170/110 and yet this patient is alive eight years later. Daniel in his report stated that irradiation probably reduces the hypertension by reducing the size of the tumor mass and thereby lessening the amount of ischemia. In our series, patient No. 10 had a reduction of hypertension but there was no palpable reduction in the size of the tumor. The concept of renal ischemia seemed quite tenable when at post-mortem examination of patient No. 2 in this series there was probably interference with circulation of the uninvolved kidney due to invasion of the inferior vena cava by tumor tissue. This concept also seemed particularly applicable in those cases where with removal of the tumor or with reduction in tumor size by irradiation the blood pressure would return to normal limits. However, the renal ischemia theory does not seem applicable to those cases where metastatic lesions in the lungs and in the liver were associated with a return of hypertension, and further, when irradiation was given over the metastatic areas the blood pressure returned to lower levels.

Originally, we[4] speculated as to whether the tumor tissue itself could be responsible for the hypertension. If this were true then it would seem logical that this could be the explanation of the above cited case. One could also reasonably expect to find a pressor substance present in these tumors. Repeated attempts on our part have failed to demonstrate the presence of any pressor substance. It would also be expected that hypertension would be present in all cases of Wilms' tumor. Such has not been our experience or the experience of other investigators. We, in our entire series, found it absent in one patient out of a total of sixteen patients for an incidence rate of 93.8 per cent; Daniel[3] found hypertension present in 77.9 per cent, and Silver[7] in 87.5 per cent. In an attempt to determine whether there was any alteration in the microscopic appearance of tumor tissue in those individuals who had marked hypertension and those who had less marked hypertension or normal pressure, we have carefully examined all tumor sections and we have not been able to detect any cellular pattern that conforms to the various clinical blood pressure manifestations.

It is interesting that irradiation in a number of our patients resulted in a substantial fall in blood pressure particularly when renal irradiation has been used to produce experimental nephritis and hypertension. The failure of a number of patients to respond with any reduction in tumor size as a result of irradiation is contrary to statements made by many authors that these tumors are extremely sensitive to roentgen-ray therapy. There does not seem to us to be any advantage in the use of preoperative irradiation except in those cases where the tumor size is such that it is surgically unmanageable and must be reduced in size.

The occurrence of hypertension with unilateral renal lesions does suggest a causative renal factor. However, the failure of hypertension to occur in all

cases of renal embryoma, and even more striking the apparent occurrence of hypertension due to metastatic lesions in organs other than the kidney, is suggestive of other factors than renal ischemia being responsible for the hypertension in these cases.

SUMMARY

The effect of the use of preoperative roentgen-ray therapy on ten patients with arterial hypertension which was found in association with embryoma of the kidney is reported.

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INCIDENCE OF MYCOTIC INFECTIONS IN CHILDREN WITH ACUTE RESPIRATORY DISEASE

FRANCES C. WHITCOMB, M.S., ALBERT MILZER, PH.D., M.D., AND
RALPH H. KUNSTADTER, M.D.
CHICAGO, ILL.

WITHIN the past decade the concept that pulmonary calcifications are almost invariably of tuberculous origin has been challenged. In 1942 Aronson, Saylor, and Parr,[1] on the basis of tuberculin and coccidioidin tests, demonstrated that coccidiomycosis is probably the cause of pulmonary calcification in negative tuberculin reactors among the Indian children in the Southwest. Long and Stearns[2] found that inductees from the East Central part of the United States had a greater incidence of pulmonary calcifications than inductees from other parts of the country. C. E. Smith[3] suggested that histoplasmosis might be the cause of pulmonary calcification in negative tuberculin reactors in the East Central and Middle Western parts of the United States. Christie and Petersen[4] and Palmer[5] showed that a correlation exists between histoplasmin sensitivity and pulmonary calcification in individuals with negative tuberculin skin tests. Bunnell and Furcolow[6] have pointed out that whenever extensive search for histoplasmosis is made there is a marked increase in the number of cases reported. They reported ten proved cases of histoplasmosis; two of the ten patients recovered.

The purpose of the present study was to conduct skin tests and cultural and serologic studies for pathogenic, systemic fungi in children with acute respiratory disease, including pneumonia. Special note was made of children with a history of allergy. Cross reactions between histoplasmin and other fungus antigens and the effect of skin testing on patients under treatment with antibiotics were also noted. The studies were made on patients admitted to the Sarah Morris Hospital for children. Emphasis was placed on children whose roentgenograms showed early pulmonary infiltrations as well as nodular, focal, or fibrotic lesions. The children ranged in age from 3 weeks to 14 years. A total of 211 children were studied. Sixty-three had clinical and x-ray findings of pneumonia, while seventy-two had acute upper respiratory infections. The remaining seventy-six children had no evidence of infectious disease, and these served as controls. All of the children were skin tested and cultured for pathogenic bacteria and fungi. Complement fixation tests were done only on the children with x-ray evidence of pneumonia and positive skin tests.

As a result of these studies three proved and two presumptive cases of fungus infections were demonstrated: (1) a case of benign histoplasmosis with symptoms of atypical pneumonia to be described fully elsewhere[12]; (2) a fatal

From the Department of Bacteriology and Virology, Medical Research Institute, and the Sarah Morris Hospital for Children, Michael Reese Hospital, Chicago.

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infection due to an unidentified fungus producing granulomatous lesions of the lung, liver, and kidney; (3) *Candida albicans* infection of the lung associated with malnutrition; and (4) two children whose x-ray findings and clinical symptoms were compatable with a cases of geotrichosis previously reported.[7]

MATERIAL AND METHODS

The children were routinely skin tested with histoplasmin,* blastomycin,* coccidioidin,† torulin,‡ and tuberculin (PPD).§ These were prepared from the mycelial phase of the following fungi, respectively: *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis*. They were used in dilutions of 1-1,000. PPD was used in dilution of 0.0001 mg.

The antigens were injected intracutaneously in 0.1 c.c. amounts into the volar surface of the forearm. A separate set of syringes and needles was used for each antigen. The skin tests were read at the end of forty-eight hours, at which time both induration and erythema were noted and measured. Reactions of 5 mm. or more of induration measured forty-eight hours after injection were considered positive. All others were interpreted as negative. The injections were done by the same person, and the skin tests were read and measured independently by two of us.

Chest x-rays were made routinely of children with acute respiratory disease on standard x-ray films (8 × 10 inches or larger). The films were read by the roentgenologist of Michael Reese Hospital without knowledge of results of the skin tests.

Each child was routinely cultured with a nasopharyngeal swab on media suitable for growth of bacterial as well as fungus pathogens. Repeated gastric lavage, blood, stool, and, in some instances, bronchial secretions in selected cases whose x-ray showed pneumonic infiltrates were cultured. All specimens were collected in sterile containers and planted immediately. A thorough search was made for the tubercle bacillus using Petragnani and egg yolk media, guinea pig and mouse inoculations.[8] Fungus cultures were planted in duplicate on plates containing cystine brain-heart infusion agar with 20 and 40 units of penicillin and streptomycin per cubic centimeters respectively. One plate was incubated at 37° and the other at 25° C. Littman's media,[9] potato dextrose, and Sabouraud's media were also inoculated with each specimen and incubated at 25° C. Cultures for actinomyces were made on beef infusion agar using the spray dish technique.[10]

Serum was drawn from patients with positive fungus skin reactions and x-ray findings of pneumonic infiltrates for fungus complement fixation tests. The technique of Tenenberg and Howell was used.[11] Complement fixation tests were done on approximately 75 per cent of positive fungus skin test reactors with pneumonic infiltrates. Histoplasmin and blastomycin antigens for the

*Furnished through the courtesy of Dr. Arden Howell of the United States Public Health Service.

†Furnished through the courtesy of Dr. Charles H. Smith of Stanford University.

‡Furnished through the courtesy of Eli Lilly & Co.

§Furnished through the courtesy of the Tuberculin Institute of Chicago and Cook County.

complement fixation tests were furnished by Eli Lilly and Co. Doubtful and positive results were repeated using H15 histoplasmin and B7 blastomycin antigens.

RESULTS

The results of the fungus and tuberculin skin tests in the three groups of children studied are summarized in Table I. As shown in Table I, no significant difference was found between the three groups of children studied. All positive skin tests for the fungus antigens were obtained during the acute stage in children with respiratory disease. Approximately 25 per cent of the negative reactors were given repeat skin tests after two weeks with negative results. An additional 15 per cent were retested six weeks to three months after the initial test, again with negative results.

TABLE I. SUMMARY OF RESULTS OBTAINED WITH SKIN TEST ANTIGENS IN TWO HUNDRED ELEVEN CHILDREN WITH VARIOUS CLINICAL FINDINGS

SKIN TEST ANTIGEN REACTION	NO. WITH EVIDENCE OF PNEUMONIA	NO. WITH UPPER RESPIRATORY INFECTIONS	CONTROLS (NO EVIDENCE OF INFECTIOUS DISEASE)
Histoplasmin-negative, tuberculin-positive	7	13	13
Histoplasmin-positive, tuberculin-positive	1*	3	4
Histoplasmin-positive, tuberculin-negative	3	3	3
Blastomycin-positive, tuberculin-negative	1	0	0
Blastomycin-positive, tuberculin-positive	1	0	1
Torulin-positive only	0	1	1
Geotrichum-positive only	1	0	0
Geotrichum-positive, coccidioidin-positive	1	0	0
Negative reactors	48†	52	54
Total no. tested	63	72	76

*_H. capsulatum_ was isolated and a positive histoplasmin complement fixation test was also demonstrated (Case 1).

†Includes two patients who died of miliary tuberculosis.

Three positive cultures of significant pathogenic fungi were obtained. One strain of *H. capsulatum* was isolated from the blood during the acute stage from a child (Case 1) with "atypical pneumonia." This patient also had a positive complement fixation and skin test for histoplasmosis. This case is discussed in greater detail below. An unidentified fungus was isolated from a fatal case with granulomatous lesions of the lung, liver, and kidney (Case 2). Finally, *C. albicans* was isolated repeatedly from an infant with pneumonia and malnutrition. Although about 5 per cent of the nasopharyngeal cultures of the three groups of children were positive for *C. albicans*, we believe that the isolation of *C. albicans* in Case 3 is significant because this fungus was isolated repeatedly in predominant numbers from gastric lavage, bronchial secretions, and stool cultures of this child. Furthermore, he responded to therapy with large doses of iodides. Negative results were obtained in cultures for other pathogenic fungi. The usual pathogenic bacteria were recovered in throat cultures of the group of children with acute upper respiratory tract infections. No significant pathogenic bacteria were isolated in most instances from the pneumonia group. Negative results were obtained in complement fixation tests with fungus antigens except for the positive histoplasmosis in Case 1. The following is a

brief abstract of the clinical records of the three proved and two presumptive cases of fungus infections encountered during the present study.

CASE 1.—The patient, J. G., a Negro boy aged 12 years, had numerous admissions into Sarah Morris Hospital with a diagnosis of rheumatic heart disease. He was readmitted September 4 after a vacation at a summer camp where he developed an acute respiratory infection. At this time he was positive to histoplasmin (7 mm. induration) and tuberculin (13 mm. induration). The tests for other fungus antigens were negative. Complement fixation tests were positive for histoplasmin only on Dec. 1, 1948 (4 plus), December 20 (3 plus), and April 2, 1949 (2 plus). On November 17 he was readmitted with a diagnosis of atypical pneumonia. He was now positive to histoplasmin (20 mm. induration) and tuberculin (10 mm. induration). Other fungus antigens remained negative. The roentgenogram revealed a large patch of parenchymal infiltration in the left midlobe. *H. capsulatum* was isolated from a blood culture drawn November 17. Cultures of bronchial secretions, gastric washings, and stools were negative for *H. capsulatum* and the tubercle bacillus. Guinea pig and dba mice inoculations for tubercle bacillus were also negative. The bronchial secretions and gastric lavages were inoculated into two groups of six white mice each, which were sacrificed after varying intervals. One mouse inoculated with bronchial secretions and sacrificed after six weeks revealed a few tubercle-like lesions in the liver and spleen from which *H. capsulatum* was isolated. This case is reported fully elsewhere.[12]

CASE 2.—The patient, N. C.,* a 3-year-old child, had been admitted into the hospital at various times with anemia, enlarged lymph nodes, splenomegaly, and skin lesions. He was readmitted in September, 1946. At this time the Mantoux test formerly negative became 3 plus. His abdomen was distended. A paracentesis was done, and the fluid obtained was examined and cultured for the tubercle bacillus with negative results. He received x-ray therapy and after a stormy course was discharged with the diagnosis of tuberculous peritonitis. He was admitted once more in November, 1946. The clinical findings and x-ray were compatible with osteomyelitis. The Mantoux and histoplasmin skin tests were negative at this time.

His final admission was on May, 1947. He had large white patches in the mouth, and the liver was markedly distended. An exploratory operation was done and a large abscess filled with caseous material was seen in the liver. No organisms were seen on direct smear. The pus was cultured and an unidentified fungus was isolated which grew in cream to gray-colored colonies after incubation at room temperature or 37° C. for five days.

The patient went downhill rapidly and died. At autopsy the lungs, liver, and kidney showed numerous granulomatous lesions. The same fungus was isolated. Microscopic sections showed gram-positive mycelia in the lungs. The organism isolated is not one of the known pathogens and so far has not been identified. Mice inoculated with the organism developed abscesses in the skin, peritoneum, and liver. The patient's brother died of the same type of disease two years previous with similar findings at autopsy. Sections of the tissues of the latter showed no mycelia.

CASE 3.—L. W., a 7-month-old Negro male infant, was transferred to this hospital with pulmonary pathology involving the right apex suspected of being either pneumonia or tuberculosis. His emotional and somatic development were retarded. *C. albicans* in predominating numbers was isolated repeatedly from

*This case is reported with the permission of Dr. Philip Rosenblum, attending physician of Sarah Morris Hospital.

gastric lavage, bronchial secretions, and stool cultures. Skin tests with the various fungus antigens and tuberculin were negative except for Candida. It was noted that he had repeated asthmatic attacks. He was found to be sensitive to both human and cow's milk. A diagnosis of food allergy with secondary pulmonary infection due to *C. albicans* was made. The patient began to improve gradually with dietary regulation and large doses of iodides.

CASE 4.—The patient, R. Y., aged 6 years, had a fever of six months' duration. He was a thin, white male child who appeared chronically ill. The initial signs of the onset of illness were a sore throat and coryza. He developed a productive cough. Three weeks after onset of fever the x-ray showed lung pathology. Streptomycin therapy was instituted with no effect. The sputum was white and mucoid but never blood-tinged. The patient lived with his family near a stone quarry and had never left Kankakee, Ill. His skin test remained negative to all fungus antigens and repeated cultures were negative for pathogenic fungi. Because of the similarity of this case, both clinically and in x-ray findings, to a case of geotrichosis reported by one of us,[7] it was decided to skin test the patient with a broth filtrate of geotrichum. He was injected intradermally with 0.1 c.c. geotrichum broth filtrate in one arm, and the same amount of the uninoculated media in the other arm. He was positive with hard induration of 10 mm. to geotrichum while the control inoculation was negative. His entire family were all positive to geotrichum with induration ranging from 10 mm. to 20 mm. Treatment with potassium iodide was instituted. The lung fields cleared slowly with some residual pulmonary fibrosis and he recovered. These cases are to be reported in detail elsewhere.

CASE 5.—B. Y., aged 4 years, and a sister of Case 4, developed mild respiratory symptoms in June, 1947, at about the time her brother became ill. X-ray of the chest revealed enlarged hilar lymph nodes but no pulmonary infiltrations. Subsequent films taken during the next six months revealed pulmonary infiltrations in both lung fields similar to Case 4. During this time she had a mild cough, but appeared well. On Feb. 11, 1948, she began taking large doses of saturated potassium iodide and when seen on April 1, 1948, was perfectly well. An x-ray at this time showed complete clearing of the pneumonic process. A skin test with geotrichum antigen showed a 2 plus reaction, while other fungus antigens were negative. Nasopharyngeal smears and cultures were negative. A follow-up examination on Sept. 18, 1948, revealed a well child.

DISCUSSION

The object of the present study was to investigate the role of mycotic infections in respiratory tract diseases of children based on cutaneous, serologic, and mycological findings. A summary of the results obtained with skin test antigens in 211 children with various clinical findings is shown in Table I. The children were arbitrarily divided into three clinical categories: (1) those with pneumonia; (2) those with acute upper respiratory infections; and (3) a control group comprising children with no evidence of infectious disease.

As shown in Table I the results of the skin reactions of the three groups were essentially the same. The total positive reactors to the fungus antigens in the three clinical groups were 12.7 per cent, 9.7 per cent, and 11.8 per cent, respectively. Also no significant difference is seen if all children with respiratory infection (total 135) are compared with the control group. The incidence of positive reactors in the former is 11.1 per cent, while it is 11.8 per cent in the latter. Positive fungus skin tests were obtained only during the acute stage in

children with respiratory diseases. An average of 8 per cent of the children in the three groups had positive histoplasmin skin tests, and they ranged in age from 3 to 13 years. In this connection it is of interest that Bendenkopf and associates[13] found that the histoplasmin sensitivity in university students resident of Chicago was 10 per cent for the age group 15 to 19 years.

Only about one-half of the children in the pneumonia group had clinical findings of pneumonia in addition to positive radiologic evidence. In this group no significant pathogenic bacteria were isolated in most instances. On the other hand, in most of the children with acute upper respiratory infections, the usual pathogenic bacteria such as beta hemolytic streptococci, coagulase-positive *Staphylococcus aureus*, pneumococci, etc., were isolated from nose and throat cultures.

Four children, representing the three categories, showed some cross reaction between histoplasmin and blastomycin. No false positive skin reactions were noted in individuals under penicillin or streptomycin therapy. It is of interest to note that only nine of the 211 children tested gave a history of allergy. Six of the allergic children were nonreactors. One was histoplasmin-positive and tuberculin-negative; one was positive to both histoplasmin and tuberculin, while the third was positive to blastomycin only.

Bunnell and Furcolow[6] cited three cases in which skin sensitivity did not appear before the forty-sixth day after onset of illness. Twenty-five per cent of the negative reactors in our series who were given repeat skin tests after two weeks remained negative. In only about 15 per cent of the pneumonia group was it possible to do repeat skin tests six weeks to three months after the first test, and again the results were negative. Perhaps additional positives would have been found if it had been possible to carry out more repeat skin tests after a longer interval of time.

During the course of these studies three proved and two presumptive cases of fungus infection were demonstrated. The first was a case of primary histoplasmosis with clinical and x-ray findings of atypical pneumonia. This patient also had a positive complement fixation and skin tests for histoplasmosis. Tests for other fungus antigens were negative. *H. capsulatum* was isolated from blood drawn during the acute stage of this case and also from bronchial secretions. Case 2 was a fatal one of a child with granulomatous lesions of the lung and liver. An unidentified fungus isolated from the lungs was pathogenic for mice. Microscopic sections showed the presence of mycelia in the lungs of this child. In Case 3 *C. albicans* was isolated from an infant suffering from pneumonia and malnutrition. This patient had negative reactions to all fungus skin test antigens except Candida and recovered following dietary regulation and large doses of iodides. Although, as already mentioned, about 5 per cent of the nasopharyngeal cultures of the three groups studied were positive for *C. albicans*, and this species is known to be part of the normal throat flora, we feel that the finding of *C. albicans* in Case 3 was significant because this organism was isolated in predominant numbers repeatedly from the gastric lavage, bronchial secretions, and stool cultures. Furthermore, he had a positive skin test for

Candida only. Finally, he responded to large doses of iodides. Cases 4 and 5 were two siblings whose x-ray findings and clinical symptoms were similar to a case of geotrichosis previously described by one of us.[7] These children showed a positive skin test for geotrichum filtrate and responded to iodide therapy although the lung fields cleared slowly with some residual pulmonary fibrosis. Skin tests with other fungus antigens were negative.

SUMMARY AND CONCLUSIONS

1. A survey to determine the incidence of systemic mycotic infections in acute respiratory diseases was done on 211 children. Each child was skin tested with various fungus antigens, and a nasopharyngeal culture was made for pathogenic bacteria and fungi. Fungus complement fixation tests as well as repeated bacterial and mycotic cultures of gastric lavage, bronchial secretions, and stools were carried out in selected cases with pneumonic involvement.

2. No significant difference was found in skin tests with histoplasmin, blastomycin, torulin, or coccidioidin in children with pneumonia, acute upper respiratory infections, or in the control group having no evidence of infectious disease. A total of sixty-three children with pneumonia were studied. Three were histoplasmin-positive and tuberculin-negative; one was histoplasmin-positive and tuberculin-positive; one was blastomycin-positive only; and one was blastomycin and tuberculin-positive. One was positive to geotrichum filtrate only and one to geotrichum filtrate and coccidioidin. Of the seventy-two children with upper respiratory infections, three were positive to histoplasmin only; three to histoplasmin and tuberculin, and one to torulin only. In the control group of seventy-six children, three were histoplasmin-positive only; four were positive to histoplasmin and tuberculin, and one was positive to torulin only.

3. Three proved cases of fungus infection were demonstrated: (1) a primary histoplasmosis with clinical findings of atypical pneumonia from which *H. capsulatum* was isolated during the acute stage; (2) a fatal infection with granulomatous lesions of the lung, liver, and kidney from which an unidentified fungus was isolated; and (3) *C. albicans* infection of the lung associated with malnutrition. Two presumptive cases of geotrichosis are described.

4. Although no significant correlation was found between systemic mycotic infections and acute respiratory disease in the present study, a fungus etiology should be considered in cases of atypical pneumonia because of the positive finding described.

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DIABETES MELLITUS IN CHILDREN

Review of 500 Cases

Henry J. John, M.D., F.A.C.P.
Cleveland, Ohio

THE diabetes seen in children may be considered to be a "pure" form of the disease, since it is uncomplicated by the degenerative changes which play a large part in the development of diabetes in older persons. Hence it is instructive to analyze the results in young patients after twenty-six years' experience with insulin treatment.

The series of 500 cases reported here has been observed over a twenty-seven-year period, so a few of them antedate the "insulin era." Some of these patients I have observed continually over many years. I have traced as many of the others as possible through correspondence with them or their families. I have no recent report on 136, or 27.2 per cent. Of the 364 patients traced, 303 are living and sixty-one are dead; i. e., 83.2 per cent of those traced are living and 16.7 per cent are dead.

INCIDENCE

The 500 cases of diabetes occurring in patients in the first two decades of life were observed in a total series of 6,000 diabetic patients (which I am reporting elsewhere). Thus, the incidence of patients under 20 years of age is 8.3 per cent. Fig. 1 shows the incidence by decades in the total series.

Age.—Diabetes mellitus may occur in a child at any age. In this series there were two children who were less than one year old when the disease appeared. Schwartzman and associates[1] collected from the literature and reviewed fifty-seven cases of diabetes mellitus in infants less than a year old. In the present series there were 263 instances in which the onset of diabetes occurred in the first decade and 237 in the second decade. Fig. 2 shows the incidence by years. This seems to indicate that the majority of cases of juvenile diabetes occur between the ages of 4 and 12 years. This finding may not be of statistical significance, but, owing to the rapid rate of growth during this period, it may be well to look for evidence in other series on this point.

Sex.—The sex distribution in this series of diabetic children was practically equal, as is true of other reported series (Table I). There were 255 (51 per cent) boys and 245 (49 per cent) girls. This finding is in definite contrast to the sex incidence of diabetes generally, as shown by my total series of 6,000 cases; among these patients of all age groups, the incidence in males was 43.3 per cent and in females 56.7 per cent.

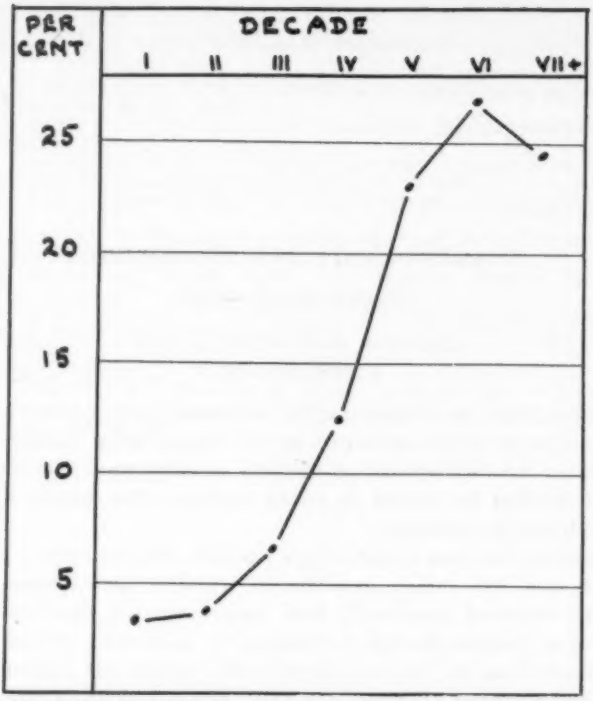

Fig. 1.—Age incidence (by decades) in 6,000 cases of diabetes mellitus.

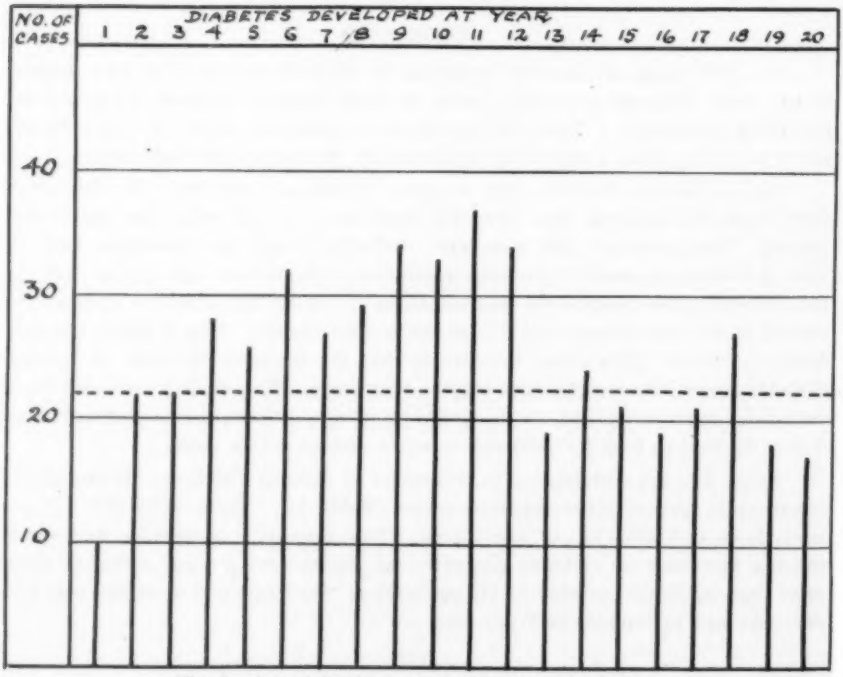

Fig. 2.—Age of development of diabetes in 500 children.

TABLE I. SEX INCIDENCE OF DIABETES IN CHILDREN

AUTHOR	NUMBER	PER CENT	
		MALE	FEMALE
Priesel and Wagner,[2]	152	52	48
Pirquet[3]	5,321	51	49
Joslin and White[4]	750	50.4	49.6
Sundby[5]	159	51	49
Total	6,382	50.9	49.1

TABLE II. THE HEREDITARY FACTOR IN 500 DIABETIC CHILDREN

CASES			PER CENT	
No history obtained	73			
History obtained	427		100	
Gentile		381	89.2	
Jewish		46	10.8	
Hereditary history of diabetes	116		27.1	
Gentile		101	23.4	(of total group)
			26.4	(of Gentile group)
Jewish		15	3.7	(of total group)
			33.5	(of Jewish group)
Familial history of diabetes	19		4.4	
Gentile		18	4.2	(of total group)
			4.9	(of Gentile group)
Jewish		1	0.23	(of total group)
			2.2	(of Jewish group)
Combined hereditary and familial history of diabetes	135		31.5	
Gentile		119	27.6	(of total group)
			31.3	(of Gentile group)
Jewish		16	3.9	(of total group)
			35.5	(of Jewish group)

ETIOLOGIC FACTORS

The two factors of prime importance in the etiology of diabetes in children are heredity and infection.

Heredity.—In the 500 cases, no history regarding hereditary or familial diabetes was recorded in seventy-three instances. Of the 427 cases in which the history was explicit in regard to this factor, there was diabetes in the hereditary background in 116. There was a familial history in an additional nineteen cases (Table II). The hereditary factor was approximately equal in the boys and the girls. The percentage of Jewish children in whom hereditary influences were present was somewhat higher than that of the group as a whole. Of the 427 children, forty-six were Jewish and there was a hereditary or familial history of diabetes in sixteen of these, or 35.5 per cent (as contrasted with 31.5 per cent for the entire group). My impression is that the influence of heredity may be more pronounced than is indicated by these percentage figures, since it has been my experience repeatedly that in children whose history showed no diabetes in the family at the time of onset, continuous follow-up has later revealed the presence of diabetes in some other member of the family. Hence I would venture to estimate the actual incidence of an hereditary tendency in diabetic children as about 40 per cent. The incidence as given by other

TABLE III. THE HEREDITARY FACTOR IN DIABETIC CHILDREN (OTHER AUTHORS)

AUTHOR	CASES	FAMILIAL AND HEREDITARY DIABETES (%)
Friese and Jahr[6]	60	11.6
Toverud[7]	47	17
Lion and Moreau[8]	100	23
Priesel and Wagner[2]	108	27
Host[9]	50	30
Ladd[10]	35	37
Joslin and White[4]	750	40
Schwartzman et al.[1]	28	43
Collens and Grayzel[11]	10	50
Smyth[12]	31	54

TABLE IV. THE FACTOR OF INFECTION IN 500 DIABETIC CHILDREN

TYPE OF INFECTION	TIME OF ONSET OF DIABETES FOLLOWING INFECTION								
	DAYS						UNDER 1 YEAR	NOT STATED	TOTAL
	1-10	11-20	21-30	31-40	41-50	51-60			
Mumps	5	1	2			1	3	25	37
Influenza	9	7	7	2		5		3	33
Measles	2	1	2	1		1	2	2	11
Dysentery	1	1	1					2	6
Pneumonia			4		1		3	2	10
Intestinal toxemia								3	3
Boils	1	1	1						3
Tonsillitis	1	1		1		1			4
Nephritis								2	2
Glandular fever			2		1				3
Jaundice	2	1							3
Septic endocarditis								1	1
Poliomyelitis			1				1		2
Abscessed teeth				1					1
Infections (nonspecific or unknown type)	1	1	1					23	26
Pyelitis			1					1	2
German measles	1								1
Scarlet fever	2	1	1					1	5
Mastoiditis			1					1	2
Whooping cough			1	1		1	1		4
Chicken pox	2		2						4
Otitis media			1						1
Total	27	16	27	6	2	9	10	67	164

authors reporting on small series varies from 11 to 54 per cent (Table III). Joslin and White,[4] who reported a series of 750 cases, found the incidence to be 40 per cent.

Infection.—Infections of various types play a definite role in the causation of diabetes in children, as has been amply demonstrated in literature on this subject.[13] The common observation of the onset of diabetes within ten to thirty days following various childhood infections certainly furnishes presumptive evidence that the infections were a factor of importance in the development of these cases. In the present series of 500 cases, there was a history of recent infection in 164 instances (Table IV). In eighty-seven, the diabetes appeared within sixty days after the infection; in ten, within one year, and in sixty-seven, the exact time of onset in relation to the infection was not stated. Thirty-seven cases developed following mumps and thirty-three after influenza.

There were twenty-six cases after infections of nonspecific or unknown type. Other infections which were followed by diabetes in this series were measles, dysentery, pneumonia, intestinal toxemia, boils, tonsillitis, nephritis, glandular fever, infectious jaundice, septic endocarditis, poliomyelitis, abscessed teeth, pyelitis, German measles, scarlet fever, mastoiditis, whooping cough, chicken pox, and otitis media. The time of onset and the distribution of cases following these infections are shown in Table IV.

The presence of a history of recent infection in 164 cases (32.8 per cent) in this series is in keeping with the observations of other authors, some of whom report a higher percentage. Friese and Jahr[6] stated that in nearly three-fourths of their series of sixty diabetic children they could demonstrate that diabetes developed shortly after an infection. Fischer[14] reported that the onset of diabetes in his series was immediately traceable to infection in approximately 35 per cent of the cases. Landabure and Magdalena[15] showed that acute infectious diseases had preceded diabetes within ninety days in 23 per cent of their cases. Adams[16] called attention to the fact that the incidence of diabetes mellitus increases in the fall, winter, and spring, when infections are most common. Jones[17] reported a high incidence of cases of diabetes following an influenza epidemic.

In the present series, the largest number of cases of diabetes following a particular infection was that related to mumps. Pancreatitis which occurs as a complication of parotitis has been reported frequently in the literature, and in a proportion of these cases diabetes is the eventual result. I have seen several such cases in adults, as well as in the children reported here. Among the authors who have reported cases of diabetes after parotitis are Gilhespie and Holden,[18] Jacob,[19] Harris,[20] and Fischer.[14]

The fact, as shown in this series, that diabetes in children develops after many types of infections, is amply corroborated by numerous reports by other authors of the onset of diabetes following various infectious diseases. Among these reports are the following: after acute colds, tonsillitis, and influenzal infections, Lierle and Porter,[21] Wendt and Peck,[22] Jones;[17] after purpura, Lefkowitsch;[23] after pyelitis, Smith;[24] after hepatitis and jaundice, Sweeney and Shirley,[25] Brems,[26] Freund and Marchand;[27] after malaria, Rau[28] and after diphtheria, Hector.[29] Numerous authors have called attention to the disturbance of carbohydrate metabolism that occurs during or after encephalitis or poliomyelitis. Kasanin and Grabfield,[30] in a study of seventeen cases, concluded that there was a fundemental disturbance of sugar metabolism in epidemic encephalitis and that this derangement persisted in patients suffering from mental sequelae of the disease. Similar conclusions have been reported by McCowan,[31] Brugsch, Dressel, and Lewy,[32] Aschner,[33] Karplus and Kreidl;[34] Nordmann[35] reported hyperglycemia in poliomyelitis and Schwartzman and associates[1] found diabetes associated with neuropathy in six of forty-eight cases. A few authors have attempted to show a relationship between syphilis and diabetes, but the general concensus is that syphilitic infections are of no significance as an etiologic factor in diabetes. In this series there was no case in which syphilis could have been a predisposing factor.

MECHANISM OF INFECTION IN PRODUCTION OF DIABETES

The question is unanswered as to why infection precipitates diabetes in one child and does not do so in ninety-nine others. Is it that the child who becomes afflicted with diabetes had a decreased insulinogenic reserve which was exhausted by the added strain of the infection? Is it that in the individual instance in which diabetes appears, the particular predisposing infection caused a more virulent toxemia than in the usual case? Perhaps both of these factors, and others not yet recognized, are important.

One fact that is well established is that infection affects the function of the pancreas adversely. In a diabetic child whose condition is well under control, for example, on a dosage of 20 units of insulin daily, a febrile condition may so upset the picture that the dosage must be increased to 80 units to control the hyperglycemia. Knowing that this is true in the diabetic child, it is easy to imagine a similar situation (and there is clinical and experimental evidence to support this assumption) in the nondiabetic child during an infection.

The possibilities usually considered to explain the decreased sugar tolerance during an infection, both in diabetic and nondiabetic individuals, are: (1) reduced insulin output or a prior decreased insulinogenic reserve; (2) inability of the liver to store glycogen readily; (3) interference with the action of insulin; (4) derangement of the mechanism of nervous control of sugar metabolism; (5) an increased output of epinephrine or of pituitary secretion which inhibits the effect of insulin. Opinions differ considerably as to which of these factors is mainly responsible, alone or in combination. It would appear to me that interference with the action of insulin, either by toxic products or by increased secretion of suprarenal or pituitary hormones antagonistic to insulin, is the most likely probability. If the liver damage were of prime importance, hyperglycemia would be encountered more frequently; furthermore, in patients with marked cirrhosis of the liver there is no hyperglycemia. Labbé and Boulin[36] in a study of nondiabetic patients during acute infections, found alimentary glycosuria in 75 per cent. The disturbance in glucose regulation did not parallel the severity of the infection, and there was no sign of insufficiency of liver function. They stated: "It is possible that recurrences of this transient disturbance of glucose balance create a true diabetes more frequently than believed." Lawrence[37] suggested, on the basis of experimental and clinical evidence, that toxins and infections antagonize insulin action by the stimulation of the thyroid and suprarenal glands. A contrary opinion has been stated by Fukuda and Itabashi;[38] they believe that hyperglycemia during infection in febrile diseases is caused by the action of bacterial toxins on the central control mechanism and not by peripheral action on the suprarenals and on the liver.

Although many questions remain as to the mechanism of the influence of infection on development of the diabetic state, the evidence, both clinical and experimental, that the carbohydrate metabolism is disturbed during infections is quite conclusive. A typical report is that of Williams and Dick,[39] who studied the carbohydrate metabolism in 108 patients with infections such as scarlet fever, diphtheria, pneumonia, influenza, measles, erysipelas, encephalitis, mumps,

epidemic meningitis, poliomyelitis, and acute tonsillitis, and in twenty-nine rabbits and three dogs in which infections were produced experimentally. Temporary glycosuria occurred in 41 per cent of the animals, in six animals this decreased tolerance lasted for several weeks or months and required treatment. The animals also showed an increased amount of dextrose in the urine during the period of acute infection. Necropsies on the animals that died revealed microscopic evidence of degeneration in the islets of Langerhans.

In view of the large number of cases of diabetes which occur in children after infections, it would be well for pediatricians to examine the urine for sugar once a week for four to six weeks after such an illness. If this were done, diabetes would be discovered early in many instances, with great advantage to the children concerned. In the earliest stage, the process affecting the islands of Langerhans may still be reversible, whereas in later stages it becomes irreversible and the pancreatic damage becomes permanent. The earlier the recognition of the insulinogenic weakness, the better the chance to control the condition and prevent additional damage.

MANAGEMENT OF DIABETIC PATIENTS DURING ACUTE INFECTIONS

The two cases which follow illustrate the importance of adequate protection of the diabetic child during intercurrent infections.

CASE 1.—Fig. 3 shows the course of the diabetes and the treatment required for its control in a patient who contracted the disease at the age of 8 years. With adequate treatment, the diabetic condition improved sufficiently that all insulin could be discontinued. He presented a normal fasting, noon, and evening blood sugar and was sugar-free on diet alone on repeated examinations. Then he contracted measles. He lived in a small town and his physician did not appreciate the change in the glucose metabolism caused by the infection and did not reinstate insulin during this period. When I saw him a few weeks later, the blood sugar had increased to almost 500 mg. per cent and he displayed signs of severe acidosis. Insulin had to be reinstated, and in large doses, and now, nearly eighteen years later, he is still required to take large quantities of insulin because of the inadequate management of the diabetes during the acute infection. This apparently caused permanent damage which is irreversible.

CASE 2.—In this instance (Fig. 4), the infection and its subsequent aggravation of the diabetes were properly considered and managed. This boy was 7½ years old in 1936 when he first developed diabetes. At the beginning, the blood sugar was high morning, noon, and light, and insulin had to be increased up to 50 units daily. After a month and one-half, all insulin could be discontinued for a period of three months, during which the three antecibal blood sugars were normal. After this, insulin had to be resumed, and in 1938, at the age of 9½ years, he was taking 10 to 18 units of insulin and 12 to 15 units of protamine zinc insulin a day. At that time he had mumps. With increased insulin dosage (to 40 units), there was only slight elevation of the blood sugar. Afterward, the dosage was reduced to 30 units. Six years later he had a second attack of mumps. By this time his diabetes had increased in severity (possibly owing to dietary indiscretion) and he was taking 150 units of insulin daily. However, the onset of the infection required only a minimal increase in the insulin dosage. The blood sugar during the infection and two years later showed reasonable control of the diabetic condition, since two out of three determinations were at or near the normal level.

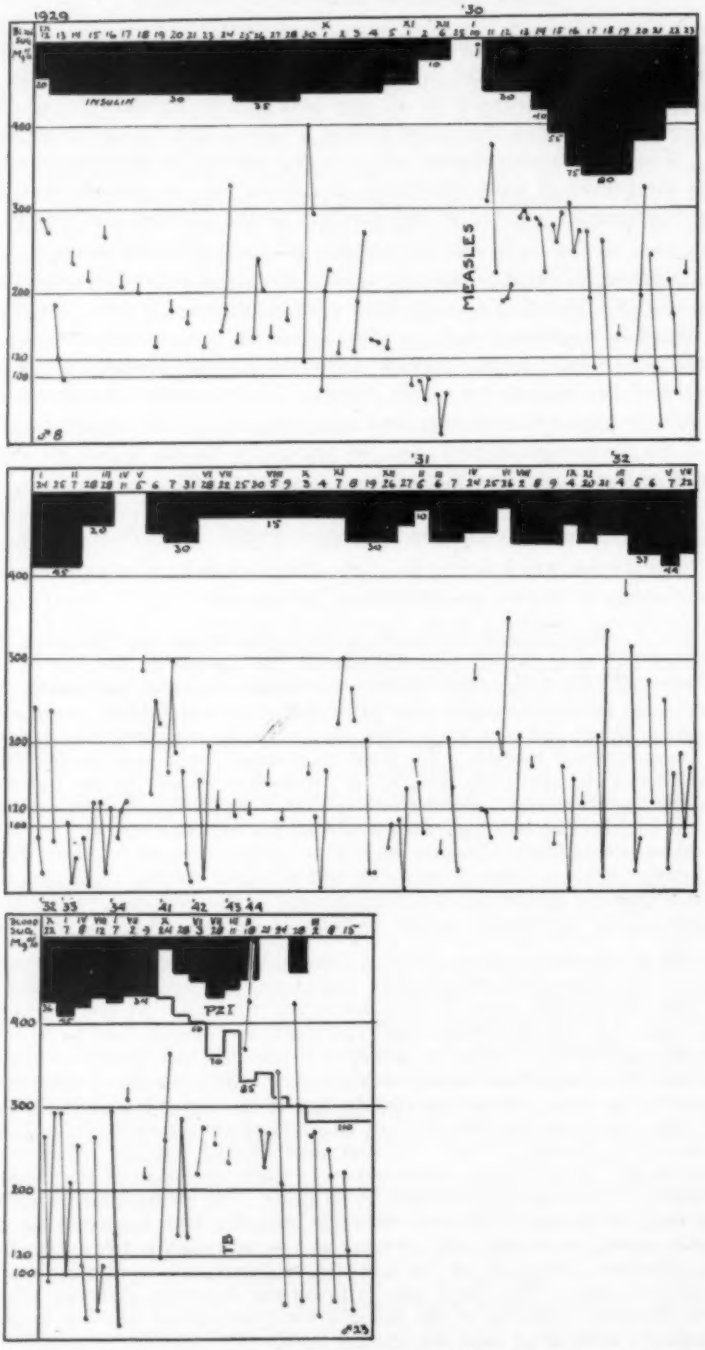

Fig. 3.—Effect of infection (measles) on the diabetic status in a boy, aged 8 years.

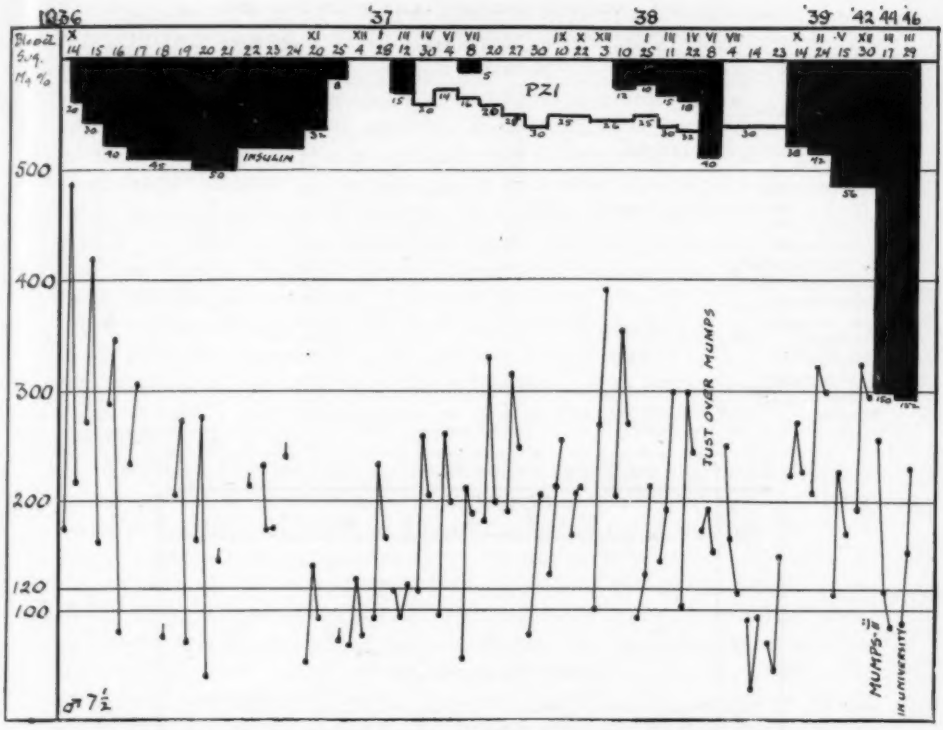

Fig. 4.—Effect of infection (mumps) on the diabetic status in a child, aged 9½ years, when counteracted by adequately increased insulin dosage.

CONTRAST OF ETIOLOGIC FACTORS IN ADULTS AND CHILDREN

As already stated, heredity and infection apparently are the most important etiologic factors in juvenile diabetes; whereas in older patients obesity and degenerative diseases obviously play a predominant role. This is clearly shown in the ensuing discussion of glucose tolerance tests, obesity, circulatory disorders, and hyperthyroidism in groups of children and of adults.

Glucose Tolerance Tests in Children and Adults in Various Affections.—In 1934, I published a series of 192 glucose tolerance tests[40] performed on patients under 20 years of age. Some of these tests were made for diagnostic reasons, others purely for scientific information. It seems pertinent here to recapitulate the results of this study, which are shown in Table V. In this group of juvenile individuals, 81.7 per cent showed normal glucose tolerance curves, whereas in a group of 1,535 adults subjected to a similar study, normal curves were obtained in only 61.5 per cent. Fig. 5 shows graphically the trend of normal and diabetic curves of glucose tolerance according to age in the total series of 1,727 cases. This chart corroborates the information shown in Fig. 1 on the age incidence of diabetes. The findings in regard to the increased incidence of

TABLE V. GLUCOSE TOLERANCE TESTS IN 192 CHILDREN

CLINICAL CONDITION	GLUCOSE TOLERANCE		PER CENT		TOTAL TESTS
	NORMAL	DIABETIC	NORMAL	DIABETIC	
Obesity	12	2	86	14	14
Hyperthyroidism	14	3	82	18	17
Hypothyroidism	10		100		10
Hypopituitarism and dwarfism	40	4	91	9	44
Glycosuria	35	17	67	33	52
Hyperglycemia	1		100		1
Arthritis and rheumatic disease	5	4	56	44	9
Eye affections	19	3	87	13	22
Neuropathies	6	1	85	15	7
Hyperpituitarism	1	1	50	50	2
Raynaud's disease	1		100		1
Tuberculosis	3		100		3
Skin diseases	4		100		4
Glycosuria of pregnancy	1		100		1
Cholelithiasis	1		100		1
Hypogonadism	1		100		1
Duodenal ulcer	1		100		1
Normal	2		100		2
Total	157	35	82	18	192

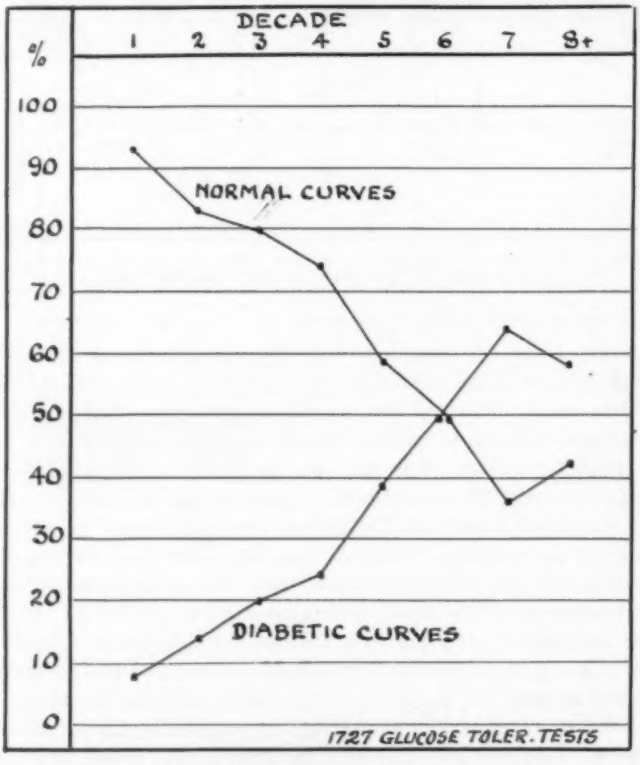

Fig. 5.—Incidence of abnormal (hyperglycemic) curves in 1,727 glucose tolerance tests, showing the increase with each successive decade of life.

diabetes with age suggest that this condition is largely a degenerative disease resulting from various affections, endocrine disturbances, infections, arteriosclerosis, and senescence.

The contrast in the incidence of diabetic-type glucose tolerance curves in adults and children is quite striking. In patients with obesity and hyperthyroidism, for instance, there were about three times as many diabetic curves in adults as in children. In the presence of glycosuria, rheumatism, and hypopituitarism, the incidence of diabetic curves was about the same in the two groups. In rheumatic conditions and chronic infections both groups showed a high incidence of abnormal curves. These differences apparently reflect functional differences between the child and the adult. The child apparently is a better physiologic unit than the adult who has been subject to repeated infections, functional stresses and strains, and dietary abuses, and thus has exhausted much of his initial insulinogenic reserve. Any intercurrent strain imposed on such a background produces greater damage than when the physiologic background is intact.

Heredity and Infection.—As has already been pointed out, heredity and infection seem to be the most important etiologic factors in diabetes in children. As shown in Table II, there was a history of hereditary or familial diabetes in 31.5 per cent of this group of children, whereas in a series of 6,000 cases, including both adults and children, the incidence of the hereditary factor was 19.13. This indicates that heredity is a much more important factor in juvenile diabetes than it is in adults with the disease. The same is true of infection, although the actual role of infection is more difficult to assess in adults. The appearance of diabetes following an acute infection is by no means rare in adults, though a history of this type is much less frequently encountered than is the case with children. In adults who have had repeated acute or chronic infections it is difficult or impossible to say how much of the general physiologic breakdown which forms the background for the development of diabetes is attributable to this cause. That it is not negligible is suggested by the fact that the incidence of abnormal glucose tolerance curves is much higher, both in adults and children, in patients with rheumatic conditions or chronic infections than it is among patients in general.

Obesity.—Obesity is not the prominent factor in the causation of diabetes in children that it is in adults, although even in very young patients it cannot be completely ignored. Fig. 6 shows the percentage incidence of abnormal, or hyperglycemic, glucose tolerance curves in adults and in children with obesity. Not all of these patients have or will have frank diabetes, but the abnormal carbohydrate metabolism represents a warning signal that the disease may develop if the obesity remains uncontrolled. This is corroborated by the strikingly similar incidence of a history of obesity in diabetic patients. In a series of 2,970 diabetic patients of all ages in whom this factor was determined definitely, it was found that 33.9 per cent were and always had been of normal weight, or at most no more than 10 per cent above normal. Conversely, 66.1 per cent were or had been at some time 11 to 220 per cent overweight. Anders and

Jameson[41] reported a series of 1,306 cases of obesity in which they found that 119, or 9.1 per cent were diabetic. Since the incidence of diabetes in the general population is, at most, no more than 2 per cent, this represents a greatly increased incidence (approximately five times the usual) in the obese.

Fortunately, because degenerative influences have not been at work over a sufficiently long period in children, overweight does not have the same coincidence with diabetes that it has in adults. Nevertheless, in 1920, Mouriquand[42] called attention to the fact that obesity or a familial history of obesity cannot be ignored in considering the problem of juvenile diabetes. He warned that incipient diabetes might be detected in children of the obese, the diabetic, and also arthritic and gouty parents. He stated that nearly all of his patients with early inherited obesity developed diabetes before the age of 40 years, but that when obesity did not develop until later in life, only 50 per cent became diabetic. In contrast to this inherited type of obesity, only 15 per cent of patients with acquired obesity developed diabetes.

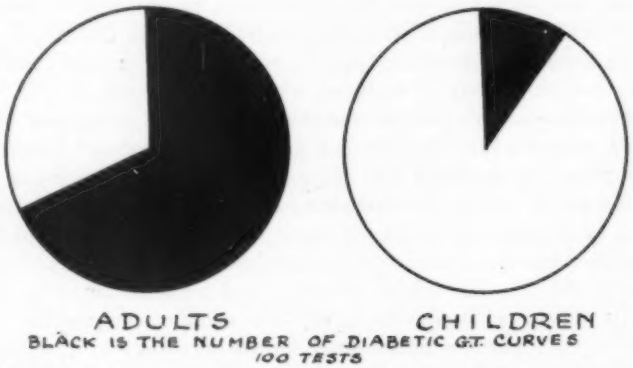

Fig. 6.—Incidence of abnormal (hyperglycemic) curves in glucose tolerance tests on obese patients, showing that the percentage is much higher in adults than in children.

Despite the relative rarity of obesity in diabetic children, it is nevertheless wise from the clinical standpoint to look upon the overweight child with suspicion and to assess carefully the carbohydrate metabolism in such individuals. The treatment of obesity in children depends, of course, on the underlying cause, which is often glandular. The problem of the prevention or control of obesity in children presents a fertile field for investigation in pediatrics and perhaps might prove to be significant from the standpoint of public health in pointing the way toward understanding and control of degenerative diseases later in life.

Arteriosclerosis.—In children, arteriosclerosis does not precede diabetes as it often does in older individuals, and for that reason cannot be considered as an etiologic factor in juvenile diabetes. Pearl Zeek[43] searched the medical literature for the past 100 years and found but ninety-eight cases of juvenile

arteriosclerosis, excluding those resulting from syphilitic infections, and, so far as could be determined, none of these children with arteriosclerosis had diabetes.

Although arteriosclerosis is not an etiologic factor in diabetes in children, it is a complication of this condition. After children have had diabetes ten years or more, arteriosclerosis begins to appear in a large proportion of cases. The literature brings out more evidence of this with each passing year. White[44] reported a series of 220 cases of juvenile diabetes in which the incidence of vascular disease in those who had had diabetes twenty years or more was 92 per cent. The vascular changes in young diabetics lead to diabetic retinitis with hemorrhages and intercapillary glomerulosclerosis, both of which are extremely serious conditions. I am not in a position to give statistical data on the incidence of arteriosclerosis in this series of children, since this requires systematic, periodic, roentgenologic study. I started such a survey, but when I entered private practice it had to be abandoned because of the cost to the patient. However, in the patients that I have followed consistently over a period of years, at least 50 per cent have developed arteriosclerosis and many of them have had the more serious sequelae, such as blindness and renal failure.

Hyperthyroidism.—Some years ago I analyzed 9,000 cases of hyperthyroidism[45] and found that 38.6 per cent of these had glycosuria and 6.88 per cent had nonphysiologic hyperglycemia (either fasting or two and one-half hours or more after meals). The patients with hyperglycemia were closely watched and protective treatment with insulin was administered. Despite this, 186 of the 620 patients remained permanently diabetic. This represented an incidence of diabetes in the 9,000 cases of 2.1 per cent. Without the protection afforded by diet and insulin during the hyperthyroidism, I believe the incidence of permanent diabetes in this group would have been much higher.

In the case of children, abnormal (diabetic-type) glucose tolerance curves occur only about one-fourth as frequently in hyperthyroidism.[40] Apparently the greater physiologic reserve or flexibility seen in the presence of other conditions, such as obesity, in the young, can withstand the grave metabolic derangement seen in hyperthyroidism and still right itself when the acute strain has been removed. In my own series of children with hyperthyroidism who were protected during and after the acute stage of the disease, none developed a frank and lasting diabetes. However, two children with slight derangement of carbohydrate metabolism during the acute stage of hyperthyroidism were told by the surgeon to forget about the hyperglycemia after thyroidectomy; both returned later with frank diabetes and are under treatment to this day.

On the whole, hyperthyroidism plays an insignificant part in the production of diabetes in children. However, when abnormalities in carbohydrate metabolism are found in the presence of juvenile hyperthyroidism, these cannot be safely disregarded, as the two cases just cited show. In fact, no matter what its cause, hyperglycemia should never be disregarded as insignificant.

TABLE VI. DURATION OF DIABETES IN 303 LIVING CHILDREN

AGE OF ONSET AND SEX		DURATION OF DIABETES IN YEARS																										TOTAL	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	M	F
	M			2								1							1					1					5	
1	F									1								1				1			1						4
	M			1			1	1						1	1				1						2	1			9	
2	F		1			1				2						1			2	1		1								9
	M					1	1								1			2			1		1						7	
3	F		3		1					3								1			1		1							10
	M		1		2			1	1	1	2								1		1	2				1			13	
4	F			1			1	1		3				1			1	1			1		1							11
	M		1					1	1				1				1	1	1	1	1				1				10	
5	F		1	1			1					1		1	1		1		1			1				2				11
	M		4	1					3								1												9	
6	F		1			1	2				1	1															1			7
	M			1					1	1		1	1			2		1		2									10	
7	F	1	1			1		1							1	2						1								9
	M		1				1		1	2			1		2		1		1								1		10	
8	F			1		1					1				1		1		1	2	1	1		1						11
	M	1		1	1			1		1		1	2			1		1						1					11	
9	F		1	1	1								1				1	1												6
	M		2	1		1					1		1		1						2	7		1					10	
10	F	1	3			1			1			1	2		1			1					2							13
	M			1						1		2	1		1	1	1						1			1			10	
11	F			1		1				1	2		1	2	1					1	1	2								13
	M	1				1				1	1		1		1	1	1	1	3	1	1		1						15	
12	F		1								2		1			2					2	1		1						10
	M									1					1		1			1								1	5	
13	F			1				1						1								1	2							6
	M						1			1						2			2			1	1						8	
14	F	1						1			1	1				1	1				1	1								8
	M		1					1		1		1								1									5	
15	F							1				1				1							1							4
	M		1																										1	
16	F			1								1						1	1		1	1			1					7
	M		2										1									2							5	
17	F							1							1				2											4
	M					1					1															1			3	
18	F			1											1			2		1						1				6
	M					1					1											1							3	
19	F							1					1																	2
	M																												0	
20	F								1															1	1					3
		6	25	16	5	11	8	11	10	20	13	12	15	6	15	14	12	14	17	12	14	15	11	5	6	4	5		1		

MORTALITY

Of the present series of 500 cases, I have been able to trace fully 364 cases, or 72.8 per cent. Of these, 303, or 83.2 per cent (of those traced) are living, and sixty-one, or 16.7 percent, died during the twenty-seven-year period of the study. Of the 303 living patients, 41.25 per cent have been followed ten years or less since the onset of the diabetes, 43.23 per cent have been followed from ten to twenty years, and 15.51 per cent have been observed for more than twenty years. A detailed analysis of these cases, according to the age at which diabetes developed, sex, and the length of survival to the present, is shown in Table VI.

In considering the sixty-one deaths in this series, it must be remembered that some of these cases date back to about two years before the use of insulin, a fact that influences the number of deaths from coma. Many of the children died in their homes in small towns, where facilities were not available for adequate treatment. Table VII shows the causes of death in this series. It is clear that coma ranks first as a cause of death in diabetic children. The second most frequent cause of death was kidney involvement which I called intercapillary glomerulosclerosis. This diagnosis was confirmed in some of these cases by necropsy; in others it was based on clinical evidence of diabetes of long duration, retinal sclerosis and hemorrhages, albuminuria, and edema.

TABLE VII. CAUSE OF DEATH IN 61 CHILDREN

CAUSE	NO. CASES
Diabetic coma	31
Intercapillary glomerulosclerosis	11
After surgery	5
Tuberculosis	4
Accident	3
Uremic coma	1
Aspiration of foreign body	1
Pneumonia	1
Meningitis	1
Ruptured appendix	1
Septicemia	1
Unknown	1
Total	61

Table VIII shows the length of time that these sixty-one diabetic children lived from the onset of their diabetes until death. The highest mortality rate was in the first year of the disease. Eighteen children, or 29.5 per cent of the sixty-one who died, succumbed within a year of onset of the diabetes. If a mother can see her child through the first year, the immediate threat to his life caused by the diabetes is greatly lessened. The initial period of adjustment to the diabetic condition and its involved problems is by far the hardest for all concerned—the patient, the family and the physician. The commonest mistake made by the family, and even by some physicians, when a diabetic child becomes ill and cannot retain food, is to withhold food and insulin, with the result that he goes into coma.

TABLE VIII. DURATION OF DIABETES BEFORE DEATH IN SIXTY-ONE CHILDREN

AT AGE WHICH DIABETES DEVELOPED	SEX	DURATION OF DIABETES IN YEARS																							TOTAL	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	M	F
1	M	1																								1	
	F												1														1
2	M																										
	F																										
3	M										1															1	
	F	1		1																							2
4	M						2		1																	3	
	F		1				1	1																			3
5	M																										
	F																										
6	M	1	1	1																						3	
	F	1																									1
7	M	1					1									1		1								4	
	F								1			1			1												3
8	M																	1								1	
	F			1					1												2						4
9	M																	1								1	
	F																										
10	M	1																								1	
	F										1																1
11	M	2																			1			1	1	5	
	F																										
12	M						1																			1	
	F		1																								1
13	M	1						1										2								4	
	F								1	1																	2
14	M	2	1				1																			4	
	F	1																									1
15	M																										
	F							1																			1
16	M		1	2																						3	
	F						1																				1
17	M	1																								1	
	F						1																				1
18	M	2				1																				3	
	F	1																									1
19	M																										
	F	1																								1	
20	M	1																									1
	F																										
Total		18	5	5		1	8	3	4	1	2	1	1	1	1	1		5			3			1	1	37	24

COMPLICATIONS

Coma.—The most serious complication and threat to the life of the diabetic child is coma resulting from acidosis. Thirty-one of the sixty-one deaths in this series were caused by this condition, representing 8.5 per cent of the 364 patients traced, or 6.2 per cent of the entire series of 500 cases.

In 1934, I reported my studies on diabetic coma in a series of 218 diabetic children.[46] In this series, covering a period of fourteen years, there were fifty instances of diabetic coma (23 per cent). Thirty-one of these children were under my immediate care during the coma; nineteen were cared for by family physicians, chiefly in small towns. Of the thirty-one patients under my care, five died; three of these were moribund on arrival and died within one hour after admission to the hospital. One died during the preinsulin period. Of the nineteen children cared for by other physicians, sixteen died and three survived. Thus the total mortality in the group I cared for was 16.1 per cent, and if the four patients just mentioned are excluded, only 3.2 per cent. The mortality in the group cared for by family physicians was 84.2 per cent. It must be remembered that these results were obtained in the early years of the use of insulin at a time when physicians were not well acquainted with this drug and were afraid to use it in large quantities.

In the years since the period covered by this earlier study, coma occurred in twenty-seven children of the present series (between 1934 and 1948). Of these, twenty-three were under my care during the emergency and four were managed by other physicians. Of the twenty-three, only one died (Table IX). Two of the four children cared for elsewhere succumbed.

TABLE IX. INCIDENCE OF DIABETIC COMA IN 500 CHILDREN

	1920-1934		1934-1948	
	CASES	PER CENT	CASES	PER CENT
Total diabetic children	218	100	282	100
Coma	50	23	27	9.5
Under personal care	31		23	
Died	5*	16.1	1	4.3
Under care of family physician	19		4	
Died	16	84.2	2	50.0

*One treated in pre-insulin era; three moribund on admission and died within one hour.

These figures reflect the picture in regard to diabetic coma in children during the last twenty-eight years. The results show that the quality of medical care during this emergency has improved tremendously, but still is not all it could be. The chief reasons for the failures are inadequate dosage of insulin and failure to use sodium chloride and glucose solutions in large quantities. Failure to handle the emergency of diabetic coma adequately in the early days of insulin use was excusable; knowledge of it was incomplete, and many physicians were timid in handling it. However, this excuse is no longer tenable, and it is significant that the two deaths in the four cases handled by other physicians in the later series occurred in one of our best hospitals, where all the facilities for adequate treatment *were* available. One of the reasons for in-

efficient treatment in a hospital is delay in getting the laboratory reports. The results of determination of blood sugar should be available in thirty minutes, for the test requires only twenty minutes. Blood sugar determinations on a patient in diabetic coma should take precedence over routine laboratory work, for the regulation of the insulin dosage in these cases is literally a matter of life or death. A patient in coma should never be left to the care of assistants or students. The physician responsible should take personal charge of the case and show his assistants how to proceed resolutely in the emergency, on the basis of confidence resulting from much experience.

Intercapillary Glomerulosclerosis.—The diagnosis of intercapillary glomerulosclerosis in this series was based largely on clinical evidence, although this was confirmed by necropsy in a few cases. Henderson and associates[47] performed post-mortem studies in a large series of diabetic patients with glomerulosclerosis accounting for 19 per cent of the deaths. In correlating their pathologic findings with clinical data, they suggested that a presumptive diagnosis of glomerulosclerosis should be based on the following factors: (1) diabetes of long standing, (2) albuminuria, (3) hypertension, (4) renal insufficiency, and (5) mixed vascular and diabetic retinopathy. Glomerulosclerosis is but rarely associated only with diabetes and albuminuria, according to these authors. Using these criteria, the evidence justified the diagnosis of intercapillary glomerulosclerosis in eleven of the sixty-one deaths in this series (18 per cent of the deaths; 3 per cent of the 364 cases traced).

The optimistic attitude that prevailed for nearly two decades after the introduction of insulin concerning the treatment of the diabetic child has, in recent years, been tempered considerably by the disconcerting reports regarding the incidence of arteriosclerosis and its serious complications in young diabetics who have had the disease ten years or longer. The future for these patients looks considerably less bright than it did ten years ago. White and Waskow[44] reported 220 juvenile diabetics who had survived twenty years or more since the onset of the disease. Of this group, 203, or 92 per cent, had vascular disease. Two had had a cerebral vascular accident; seven had coronary insufficiency; forty showed albuminuria; fifty-five had hypertension; seventy had calcified arteries; seventy-five had retinal hemorrhages; eighty-five had retinal arteriosclerosis, and six had retinitis proliferans. These authors also reported: "Since 1940 every diabetic child in our clinic who has survived fifteen years of diabetes and has come to autopsy has shown this lesion (intercapillary glomerulosclerosis), with or without pyelonephritis." Dolger[48] reported that of 200 patients subjected to regular periodic examinations, 50 per cent showed albuminuria at the time that retinopathy developed. In a group of sixteen patients who developed diabetes before the age of 10 years and in thirty-nine who developed diabetes between the ages of 10 and 20 years, all of whom had had diabetes for twenty-five years, Dolger found retinitis with hemorrhages in all.

Although I have not been able to follow personally all of the patients in this series by regular periodic examinations, I do have data on the incidence of albuminuria in a group of eighty-three patients who have continued under my

personal care over a period of years. Twenty-six (31.3 per cent) of these show albuminuria, and fifty-seven (68.7 per cent) do not. The incidence of albuminuria relative to the duration of the diabetes is shown in Table X. The interesting thing here is that the percentage incidence of albuminuria did not increase appreciably with longer duration of the diabetes, a finding somewhat at variance with the reports of others.

TABLE X. APPEARANCE OF ALBUMINURIA IN EIGHTY-THREE DIABETIC CHILDREN

DURATION OF DIABETES IN YEARS	CASES	ALBUMINURIA		NO ALBUMINURIA	
		CASES	PER CENT	CASES	PER CENT
10 or less	31	9	29	22	71
10 to 15	31	11	35.4	20	64.6
16 to 20	18	6	33.3	12	66.7
21 to 25	3	0		3	100.0
Total	83	26	31.3	57	68.7

Other Complications.—Diabetic coma and glomerulosclerosis accounted for slightly under 70 per cent of the sixty-one deaths in the present series. The other deaths resulted from surgical operation, some type of infection, or accident. Diabetes represents an additional risk in case of surgery, but if the diabetic status is carefully watched and managed during the emergency, with proper regulation of the insulin dosage according to the indications, the results are generally satisfactory. The five deaths after operation in this series are largely accounted for by the fact that the surgery was performed in small hospitals where adequate facilities for emergency management of the diabetes were lacking. There is also the possibility that two of these patients actually had diabetic coma, rather than the acute appendicitis for which operations were performed. Since the onset of diabetic coma is marked by nausea and vomiting, this diagnostic mistake is not rare among physicians without great experience in treatment of diabetes.

The importance of thorough study of the carbohydrate metabolism and its fluctuations during any intercurrent infection has already been stressed. If these sudden changes are not properly controlled, infection may be a precipitating cause of diabetic coma. In any infection in a diabetic child, there is danger of a permanent decrease in the insulinogenic reserve unless adequate protection is given at such a time.

SUMMARY

The present study reports an analysis of 500 cases of juvenile diabetes (onset of the disease during the first two decades of life) in a total series of 6,000 diabetics observed during a period of twenty-seven years. Thus the incidence of diabetes in patients 20 years of age or less was 8.3 per cent. The sex distribution in the 500 cases of diabetes in children was practically equal, with 255 (51 per cent) boys and 245 (49 per cent) girls.

Heredity and infection are evidently the prime etiologic factors in the development of juvenile diabetes. In this series there was an hereditary or familial history of diabetes in 31.5 per cent, with the incidence in forty-six Jewish children of the group somewhat higher, i. e., 35.5 per cent. Infections,

principally the acute exanthemata, play a considerable role in precipitating the onset of diabetes. In this group of 500 cases, there was a history of antecedent infection in 164. In the majority of these, the diabetes appeared within two months after the infection.

A comparison of glucose tolerance tests in adults and children and of the histories of diabetic patients in the two age groups shows the increasing importance of obesity, endocrine disturbances, and degenerative changes, particularly arteriosclerosis, in the causation of disturbances in carbohydrate metabolism and in the development of diabetes, with advancing age.

Of this series of 500 juvenile diabetics, 364 were traced to the present time. Of these, 303, or 83.2 per cent are living, and sixty-one (16.7 per cent) are dead. Of the 303 living patients, 41.25 per cent have been followed for ten years or less since the onset of the diabetes, 43.23 per cent have been observed from ten to twenty years, and 15.51 per cent have had the disease more than twenty years.

Diabetic coma was the principal cause of death in this series, accounting for thirty-one of the sixty-one deaths. Only six of these thirty-one patients were under my immediate care at the time of death; of these six, one was treated in the preinsulin era and three were moribund and died within one hour after admission to the hospital. The others were under the care of their family physicians, mostly in small towns, at the time of the emergency. The second most important cause of death was intercapillary glomerulosclerosis, which brought death to eleven of the sixty-one patients. The other deaths occurred after infections, surgical operations, or accidents. Deaths in these sixty-one patients occurred from within less than a year to twenty-four years after onset of the diabetes. The largest number died within the first year, i. e., eighteen of the sixty-one (29.5 per cent). Thirty-seven of the deaths occurred in males and twenty-four in females.

As shown by the mortality figures, diabetic coma is the most serious complication threatening the child with diabetes. According to the records in this series, as experience has been gained by physicians and as the training of younger physicians in the handling of emergencies has improved, the incidence of diabetic coma has become considerably less than in the first decade after insulin was discovered. In this series, there were 218 patients seen from 1920 to 1934, and of these, fifty are known to have had diabetic coma (23 per cent). In the period 1934 to 1948, twenty-seven patients (9.5 per cent) had diabetic coma. Of the seventy-seven patients with this complication, fifty-four were under my personal care at the time of the emergency, with a total of six deaths. Twenty-three patients received treatment for the diabetic coma by their family physicians, and in this group there were eighteen deaths.

The optimism concerning the fate of diabetic children which represented the general concensus in the years immediately following the discovery of insulin has been modified considerably in recent years by the high incidence of premature arteriosclerotic changes in these patients, leading to retinopathy and glomerular changes in the kidney which have led to blindness and early death in many instances. In this series, eleven of the sixty-one deaths (18 per cent) were due to intercapillary glomerulosclerosis.

In a series of eighty-three patients in this series whom I have been able to observe by regular periodic examinations over a period of years, twenty-six (31.3 per cent) show albuminuria. In this series, the incidence of albuminuria is not significantly higher in patients who have had diabetes for ten to twenty-five years than in the group who have had the disease less than ten years. Other authors report an increasing incidence with longer duration of diabetes.

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RENAL FUNCTION IN DIABETES INSIPIDUS

LEWIS BARTA, M.D.
BUDAPEST, HUNGARY

ALTHOUGH the rate of glomerular filtration is considerably influenced by endocrine factors,[1, 2] the amount of glomerular filtrate is usually normal in diabetes insipidus.[3, 4] Polyuria is a consequence of decreased tubular reabsorption. There are, however, cases in which the excretion of creatinine is considerably decreased.[5] This could point to a decrease of the glomerular filtration rate.

In two patients suffering from diabetes insipidus, observations were made in order to investigate the connection of glomerular filtration rate and tubular reabsorption.

CASE REPORTS

CASE 1.—Sz. I., a male patient 8 years of age, had been suffering from diabetes insipidus for eight years, when it was observed that the amount of urine that had always amounted to from 3 to 4 L. a day decreased to from 650 to 850 ml. The specific gravity of the urine remained as low as 1001 to 1002 in spite of the fact that polydypsy had ceased. Analyses of the blood revealed 362 mg. per cent chlorine, 313 mg. per cent sodium, 20 per cent nonprotein nitrogen, 190 mg. per cent cholesterol, 1.6 mg. per cent creatinine, 21 mg. per cent urea; blood pressure was 90/45 mm. Hg. In the urine there were 394 mg. per cent chlorine, 179 mg. per cent urea, 20 mg. per cent creatinine. According to double glucose and galactose tolerance tests following administration of insulin and cortical extract, carbohydrate metabolism was normal. There was slight hypoproteinemia with 3.9 Gm. of albumin and 1.9 Gm. of globulin per 100 ml. of blood. Urine creatinine per plasma creatinine was 12.5, diuresis per minute 0.5 ml., and the clearance of creatinine 6.25 ml. According to that value, the glomerular filtration rate was very low. Urinary output remained, however, normal owing to the tubular work characteristic of diabetes insipidus, i.e., urine amounted only to 8 per cent of the glomerular filtrate.

After administration of 6 gr. of sodium chloride to the patient weighing 28 kg., chlorine in the serum rose from 369 mg. per cent to 426 mg. per cent in ninety minutes. A rise of more than 35 mg. per cent is said to be characteristic of diabetes insipidus.[6] In the urine the original chlorine level of 394 mg. per cent decreased to 117, 144, 167, and 171 mg. per cent. The phenomenon was followed by diuresis as 800 ml. of urine were excreted during the next three hours. In this period urine creatinine per plasma creatinine was 8.3, diuresis per minute 4.7 ml., and the amount of glomerular filtrate 39.01 ml. Diabetes thus became manifest. In consequence of the increased rediffusion of chlorine, excretion of minerals could not be increased only by increasing the volume of urine. In spite of the percentile decrease of urinary chlorine, the absolute quantity excreted of that mineral was considerably raised.

The patient was then given 5 mg. of desoxycorticosterone acetate intramuscularly every day for three days. During this period the daily amount of urine fell, in spite of the standard diet, from 600 ml. to 300 ml. Excretion of

From the First Department of Pediatrics of the Hungarian Petrus Pázmány University.

minerals was also decreased; potassium in the urine decreased from 90 mg. per cent to 23 mg. per cent, sodium to 48 mg. per cent, chlorine to 85 mg. per cent, urea to 36 mg. per cent, and total nitrogen to 60 mg. per cent. In the plasma the following values were found: sodium 317 mg. per cent, potassium 16 mg. per cent, chlorine 390 mg. per cent, nonprotein nitrogen 20 mg. per cent. Urinary creatinine per plasma creatinine was 5.3 per 1.1 — 4.8, diuresis per minute 0.2 ml., glomerular filtrate 0.96 ml. The excretion of both urea and potassium suffered a considerable decrease following administration of desoxycorticosterone acetate. Following administration of posterior pituitary extract, the specific weight of urine rose to 1019; urinary creatinine per plasma creatinine was 88 per 1.3 — 67. After discontinuation of the extract, the specific weight of urine fell to the original value of 1001.

The latent stage of diabetes insipidus was observed for about three months; then the patient was discharged. According to a follow-up examination three months later he completely recovered from the condition. There has never been any indication of a renal lesion.

CASE 2.—Sz. K., a female patient 8 years of age, had been excreting 3 to 5 L. of urine a day for years. At admission, urinary creatinine per plasma creatinine was 10 per 0.8 — 12.5, diuresis per minute 2.4 ml., glomerular filtration rate 30 ml. The desoxycorticosterone acetate was administered intramuscularly in doses of 5 mg. a day for five days. Following this the output of urine rose to from 7 to 8 L. a day and a decrease occurred in the clearance of creatinine: Vc/Pc — 2/0.6 — 3.3. Before desoxycorticosterone acetate administration in the urine, there were potassium 40 mg. per cent, chlorine 196 mg. per cent, and total nitrogen 204 mg. per cent. After treatment the values were reduced to potassium 32 mg. per cent, chlorine 100 mg. per cent, and total nitrogen 80 mg. per cent. Chlorine in the serum was 400 mg. per cent before treatment and 410 mg. per cent after it. Posterior pituitary extract had a favorable effect; diuresis fell to 1 L. a day.

The clearance of inulin was also determined in this case. One hundred milliliters of a 10 per cent solution in saline was injected intravenously and an additional 100 ml. of the solution were infused in the next one-half hour. Blood and urine were collected every ten minutes and inulin, creatinine, and urea determined in every sample. Data are tabulated in Table I.

TABLE I

	PERIODS OF 10 MINUTES		
	1ST	2ND	3RD
Diuresis, ml./min	14.5	8.1	10.8
Inulin in urine	308	785	915
Inulin in plasma	145	157	149
V_I/P_I	2.1	5	6.1
Glomerular filtration rate, ml.	31	40.5	66
Creatinine in urine	-	5	6
Creatinine in plasma	-	0.8	0.8
Vc/Pc	-	6.2	7.5
Urea in urine	-	58	55
Urea in plasma	-	17	17
$V\mu/P\mu$	-	3.4	3.2

The diuresis following administration of inulin is partly connected with sodium chloride, partly with the effect substances of a high molecular weight exert on osmo-regulation. Patients suffering from diabetes insipidus are sensitive to similar stimuli as was well illustrated by the changes in the rate of glomerular filtration. There was little difference between the clearance rates

of inulin and creatinine, the higher values for the latter substance might be ascribed to tubular excretion. The low urea values are due to tubular reabsorption. There was little divergence between the amounts of urine excreted during the three periods in spite of the fact that the rate of glomerular filtration rose to twice the original value. This shows that the rate of tubular reabsorption increased parallel with the glomerular filtration rate.

The origin of the condition could not be cleared either from the history or by examination. There was no indication whatever of a renal lesion.

COMMENT

The first patient recovered from diabetes insipidus at the onset of puberty. Prior to this, the condition that had been manifest for many years became latent. The amount of urine was normal in this period but its specific weight remained as low as 1001 to 1002 and the excretion of both minerals and nitrogen was also low. The latter phenomenon can be partly ascribed to the fact that 5 kg. of weight was put on during the latent period. The glomerular filtration rate was very low but tubular reabsorption of water corresponded to a state of diabetes insipidus and the amount of urine excreted remained normal. The condition could be well influenced by posterior pituitary extract. Both the rate of glomerular filtration and reabsorption in the tubular system could be normalized by that substance. Nephrogenic diabetes insipidus[7] could, therefore, be excluded. The fact that there was an increase in the glomerular filtration rate following administration of sodium chloride speaks also against renal lesion. Following desoxycorticosterone acetate there was a further decrease in the glomerular filtration rate and also in the excretion of potassium, sodium, chlorine, and nitrogen, and in the tubular reabsorption of water which amounted to 80 per cent of the glomerular filtrate.

The second case could also be influenced by posterior pituitary. Polyuria was augmented by desoxycorticosterone acetate, which caused a moderate decrease of the glomerular filtration rate and a considerable reduction of tubular reabsorption. Urinary creatinine fell to 2 mg. per cent. A rediffusion of 80 per cent of the glomerular filtrate is an obligatory process[8] and as only 20 per cent of it is under neurohormonal influence, it had to be supposed that some tubular lesion due to creatinine was the cause of the passive rediffusion of the substance.[9] The supposition was not confirmed by the clearance rate of inulin as in the first period this was 2.1 with a diuresis of 14.5 ml. per minute, i.e., nearly 50 per cent of the glomerular filtrate was reabsorbed. Tubular reabsorption of 80 per cent of the glomerular filtrate may be obligatory under normal conditions but, accordnig to the inulin clearance rate, the values obtained for creatinine have to be regarded as real in the present case.

The considerable diuresis observed following administration of inulin may have been due partly to the sodium chloride injected. In this period there was a considerable increase of glomerular filtration and tubular reabsorption. In Case 2, there was, therefore, no change in the minute rate of diuresis. The effect of sodium chloride is contrary to that of desoxycorticosterone acetate following administration of which substance both glomerular filtration rate and tubular reabsorption were reduced.

According to the above, the glomerular filtration rate plays a significant role in the water and salt metabolism of patients suffering from diabetes insipidus. In Case 1, a spontaneous reduction of the glomerular filtrate occurred during the period preceding recovery and at the same time the amount of water reabsorbed in the tubules was also decreased together with the excretion of minerals and nitrogen. Desoxycorticosterone acetate increased the retention of salts and nitrogen and reduced the rate of glomerular filtration. In Case 2, the glomerular filtrate was only moderately reduced by desoxycorticosterone acetate with a parallel increase in the excretion of potassium and a decrease in the excretion of other minerals and nitrogen. In this case the tubular reabsorption of water was reduced to such a degree that a considerable increase of polyuria occurred and the condition of the patient was aggravated. It must be noted that in infants and small children, in which increase in weight owing to water and salt retention was achieved by desoxycorticosterone acetate, there was laways a decrease in the clearance of creatinine. In cachectic patients desoxycorticosterone acetate often caused loss of weight and marked polyuria.[9, 10]

According to our observation, decrease in glomerular filtration rate was followed by reduction of tubular reabsorption. The changes were not wholly parallel. In Case 1, the reduction of glomerular filtrate following administration of desoxycorticosterone acetate was more significant than that of tubular reabsorption, consequently oliguria resulted. In Case 2, the decrease of the glomerular filtration rate remained insignificant while a considerable reduction occurred in the rate of tubular reabsorption, thus polyuria appeared. It is probable that the effect desoxycorticosterone acetate exerted on the renal function of both patients was in connection with the changes in water- and salt-retaining capacity of the tissues.

SUMMARY

According to observations made on two patients suffering from diabetes insipidus, it is probable that the changes in glomerular filtration rate play a significant role in the regulation of water and mineral metabolism in diabetes insipidus. In Case 1 polyuria was controlled by a decrease in glomerular filtration and at the same time water and salt retention was increased. In this period the condition could be made manifest by administration of sodium chloride. In both cases glomerular filtration and tubular reabsorption were both decreased by desoxycorticosterone acetate. The rate of reduction of the two functions were, however, in no relation with one another so that polyuria appeared in the first case and oliguria in the second one. The effect of desoxycorticosterone acetate on renal function is probably in connection with its influence on the salt and water retention of the tissues.

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THE EFFECT OF ANTIHISTAMINIC DRUGS ON THE TUBERCULIN PATCH TEST

EDWIN L. KENDIG, JR., M.D., WILLIAM P. SPENCER, M.D., AND CARL W. LAFRATTA, M.D.
RICHMOND, VA.

THE tuberculin test is an important diagnostic aid in all tuberculosis, but it is of particular value in tuberculosis of childhood. Any drug which might conceivably interfere with this test by causing a "false negative" reaction should be investigated. Since the antihistaminic drugs have been shown to inhibit urticarial response in many dermatoses,[1, 2, 3] and since use of these drugs has become widespread, the present study was undertaken.

THE STUDY

On a group of twenty patients at the Pine Camp Hospital a tuberculin patch test (Vollmer) was performed. After forty-eight hours the patch was removed and forty-eight hours later the test was read. All the tests were positive, but to a varying degree.

Eight hours before the second patch test was applied an antihistaminic drug was instituted by mouth. Eleven patients were given antistine in dosage of 150 mg. for the first day and 300 mg. daily for the ensuing four days until the test was read. Eight patients were given pyribenzamine in the same dosage, and one had pyribenzamine 150 mg. daily for the five-day period.

RESULTS

In that group taking Antistine, the degree of tuberculin reaction was actually slightly greater in 5 instances, and in no case was less marked (see Table I). Among those taking Pyribenzamine, the degree of tuberculin reaction was slightly greater in one case and slightly less in two instances (see Table I). In none of the above cases was the difference great, and in all others there was no difference in the tuberculin reaction with and without antihistaminic drug administration. All readings were done by the same individuals in order to insure uniformity of interpretation.

TABLE I. TUBERCULIN REACTION AFTER ANTIHISTAMINIC DRUGS

DRUG	PATIENTS	MORE REACTION	LESS REACTION
Antistine	11	5	0
Pyribenzabine	9	1	2
Totals	20	6	2

The antistine and pyribenzamine were supplied through the generosity of Ciba Pharmaceutical Products, Summit, N. J.

The tuberculin patch tests were made available through the courtesy of the Lederle Laboratories, Pearl River, N. Y.

DISCUSSION

The value of the routine tuberculin test as an aid in diagnosis of tuberculosis is well recognized. In order to avoid an extra needle puncture, many physicians, particularly those treating children, employ the tuberculin patch test (Vollmer) in this manner. The pertinent question is whether or not ingestion of an antihistaminic drug at the time of the application of the tuberculin test can inhibit a positive reaction in an individual with tuberculous infection. In our study the antihistaminic drugs had no inhibitory effect on the reaction of the tuberculin patch test.

Boquet,[4] in guinea pig experiments with the earlier antihistaminic drugs, found that the tuberculin reaction was unchanged. In more recent studies Guy[5] and Criep[6] and associates found the antihistaminic drugs to be without inhibitory effect on the intradermal tuberculin test, and the latter also showed that intradermal Pyribenzamine and Pyribenzamine by iontophoresis had no effect on the reaction of the tuberculin patch test. Sarber,[7] working with guinea pigs, found that Benadryl gave a reduction in the tuberculin skin reaction, and felt that other investigators had failed to arrive at this conclusion because they had not used threshold doses.

The present study was conducted only to determine whether or not ingestion of the antihistaminic drugs inhibited the tuberculin patch test, a case finding technique widely used in pediatrics. No inhibition was noted.

SUMMARY

In a study of twenty tuberculous individuals, administration of Antistine and Pyribenzamine by mouth produced no change in the skin reaction of the tuberculin patch test.

We appreciate very much the help of those patients and members of the staff of Pine Camp Hospital whose cooperation made this study possible.

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THE BETA DISTURBANCE OF THE ELECTROPHORETIC PATTERN OF BLOOD SERUM IN POLIOMYELITIS

V. C. Kelley, Ph.D., M.D.,* Doris Doeden, M.S., T. N. Hall, M.D., and I. McQuarrie, Ph.D., M.D.
Minneapolis, Minn.

IN electrophoretic patterns of blood serum obtained by the Longsworth "schlieren scanning" technique[1] there is commonly observed in the beta globulin region of the descending boundary a disturbance which appears as a sharp spike extending indefinitely out of the picture. In a preliminary study of the electrophoretic characteristics of the blood serum in poliomyelitis reported from this laboratory,[2] it was observed that definite abnormalities in this beta disturbance commonly occurred in the patterns obtained in that disease.

Two recent epidemics of poliomyelitis in Minnesota have made it possible for us to obtain blood serum from a large number of individuals afflicted with this disease. Using this material we have now completed a more extensive study in an attempt to evaluate the significance of our preliminary observation of the occurrence of abnormalities in the beta disturbance of the electrophoretic patterns of blood serums obtained from cases of poliomyelitis.

MATERIALS AND METHODS

The blood specimens in the cases of poliomyelitis were obtained, with a few exceptions, from patients in the Department of Pediatrics of the University of Minnesota Hospitals. The normal control subjects were selected from visitors to a large pediatric out-patient clinic and included children who came to the clinic for psychiatric evaluation, dental examination, eye examination, or minor congenital anomalies. These children were all free of recent or existing disease as determined by histories and routine physical and laboratory examinations. All blood specimens drawn were morning, fasting specimens.

The serum was separated at once and stored at −30° C. until used. Before being submitted to electrophoresis, each sample was diluted with three volumes of a phosphate buffer of pH 7.8 and ionic strength of 0.1 or a veronal buffer of pH 8.65 and ionic strength of 0.1 and was then dialyzed against a large volume of the same buffer for three days.

The electrophoretic patterns of these diluted serums were then obtained after 120 minutes of electrophoresis under a potential gradient of 5.33 volts per centimeter by the "schlieren scanning" method of Longsworth.[1]

EXPERIMENTAL

In the present report, as in our previous report,[2] the changes in the beta disturbance are classified as 0 to 3+, where 0 is taken to mean no change in the

From the Department of Pediatrics, University of Minnesota.
Aided by a grant from The National Foundation for Infantile Paralysis
*Swift Foundation Nutrition Fellow.

beta disturbance (i.e., it appears as a narrow, tall peak) and 3+ is taken to mean the complete absence of the beta disturbance. 1+ indicates a definite shortening and broadening of the beta disturbance, and 2+ indicates a very marked decrease of the beta disturbance but not its complete absence. Fig. 1 shows typical electrophoretic patterns illustrating these various degrees of beta disturbance.

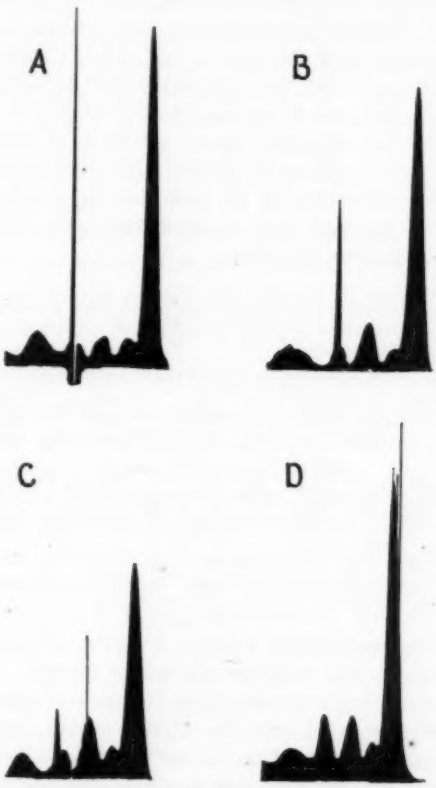

Fig. 1.—Three degrees of alteration in the beta disturbance of the electrophoretic pattern (descending boundry). *A* shows the beta disturbance appearing as a narrow spike of infinite length (O change). *B* represents 1+ change; *C*, 2+ change; and *D*, 3+ change (complete absence of beta disturbance).

A total of 252 electrophoretic experiments are included in this report. Of these, 212 are on serum samples from poliomyelitis patients, 142 done in veronal buffer at pH 8.65, and 70 in phosphate buffer at pH 7.8. The remainder are on serum samples from normal children, 20 done in each of these buffers.

The results of the electrophoretic studies done on serum samples from poliomyelitis patients are summarized in Table I. From this table it may be seen that in veronal buffer 50 per cent of the patterns showed a marked change

or absence of the beta disturbance, that is, 2+ or 3+ change, while in phosphate buffer 78.5 per cent of the patterns showed such major changes. These data are in agreement with those of our previous study[2] in that in the phosphate buffer only two patterns (2.9 per cent of the cases) showed 0 change, the other 97.1 per cent of the cases showing at least a 1+ change. The hospital charts of all of these patients were carefully analyzed in an attempt to correlate the occurrence of changes in the beta disturbance with varying clinical manifestations of the disease. No correlation was found to exist between the appearance of the beta disturbance and the age or sex of the patient, the extent of paralysis, the occurrence of bulbar symptoms, or the temperature and pulse of the patient at the time the blood sample was obtained. There is likewise but little correlation of the appearance of the beta disturbance with the duration of the disease. As shown in Table I major changes in the beta disturbance occurred more frequently in the first ten days after the onset of the disease than later in patterns done in phosphate buffer but the reverse was true in patterns done in veronal buffer.

TABLE I. THE BETA DISTURBANCE IN SERUM SAMPLES FROM POLIOMYELITIS PATIENTS

BUFFER	TIME AFTER ONSET	NUMBER OF SAMPLES	NO CHANGE		1+ CHANGE		2+ CHANGE		3+ CHANGE		PER CENT SHOWING NO OR SLIGHT CHANGE	PER CENT SHOWING MARKED CHANGE
			NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT		
Veronal	1-10 days	77	21	27.3	21	27.3	17	22.1	18	23.3	54.6	45.4
	More than 10 days	65	11	16.9	18	27.7	13	20.0	23	35.4	44.6	55.4
	Total	142	32	22.5	39	27.5	30	21.1	41	28.9	50.0	50.0
Phosphate	1-10 days	41	1	2.4	6	14.6	9	22.0	25	61.0	17.0	83.0
	More than 10 days	29	1	3.4	7	24.1	10	34.5	11	38.0	27.5	72.5
	Total	70	2	2.9	13	18.6	19	27.1	36	51.4	21.5	78.5

During the progress of these studies, it became apparent that there was a definite difference in the incidence of major changes in beta disturbance occurring in phosphate buffer as compared to veronal buffer. For this reason, a series of forty cases was subjected to parallel studies in the two buffers. In these cases the serum obtained from a particular blood sample from a poliomyelitis patient was divided into two portions, one portion being studied in veronal buffer, the other in phosphate. The results of these studies are shown in Table II. The data obtained verified our original impression that there was a much greater incidence of major abnormalities in the beta disturbance of electrophoretic patterns obtained in phosphate buffer than of patterns obtained in veronal buffer. Analysis of the data presented in Table II reveals that a 3+ change in beta disturbance occurred in twenty-five of forty cases (62.5 per cent) in phosphate buffer as compared to only eight of forty cases (20 per cent) in veronal buffer. Also of the same forty cases, ten (25 per cent) showed a 0 change in beta disturbance in veronal buffer but none showed a 0 change in phosphate buffer. In only three cases was the change in beta disturbance greater in veronal than in phosphate buffer, while in twenty-five

TABLE II. INFLUENCE OF BUFFER ON OCCURRENCE OF CHANGE IN BETA DISTURBANCE

PATIENT	CHANGE IN BETA DISTURBANCE		PATIENT	CHANGE IN BETA DISTURBANCE		PATIENT	CHANGE IN BETA DISTURBANCE	
	PHOSPHATE	VERONAL		PHOSPHATE	VERONAL		PHOSPHATE	VERONAL
R. H.	2+	2+	G. B.	3+	3+	R. F.	3+	3+
R. W.	1+	0	A. K.	2+	0	M. N.	3+	1+
L. S.	1+	2+	E. C.	2+	2+	S. A.	3+	2+
J. S.	1+	0	J. S.	3+	2+	J. B.	2+	2+
K. B.	3+	1+	R. W.	3+	3+	A. B.	2+	1+
J. L.	2+	2+	G. S.	3+	2+	R. S.	3+	1+
T. W.	2+	0	R. B.	3+	0	A. E.	3+	1+
W. W.	2+	0	B. M.	1+	0	E. J.	3+	1+
J. G.	3+	3+	M. H.	3+	2+	H. R.	3+	1+
H. E.	2+	2+	W. F.	3+	3+	E. D.	3+	1+
S. M.	3+	0	G. B.	2+	3+	J. H.	3+	0
R. S.	3+	0	J. E.	3+	3+	L. R.	1+	2+
W. M.	3+	2+	J. L.	3+	1+			
T. N.	3+	3+	P. C.	3+	1+			

cases it was greater in phosphate than in veronal. In veronal buffer 50 per cent of these forty cases showed a major change in beta disturbance (2+ or 3+ change), while in phosphate buffer 87.5 per cent showed a similar change. These figures are in good agreement with the data obtained in the larger series which are shown in Table I.

In order to ascertain whether or not results such as those obtained with poliomyelitis serums (Table I) represented significant deviations from the normal, a series of serum samples from normal children was studied electrophorectically in both phosphate and veronal buffers. Table III shows the results of these studies. It is apparent from these data that in the case of serums from normal subjects, as well as in the case of serums from subjects with poliomyelitis, the type of buffer used influences profoundly the appearance of the beta disturbance of the electrophoretic pattern. It is also apparent that the beta disturbance of normal serum is not necessarily a tall, narrow, spike but that it may vary over the entire range from such an appearance to complete absence. There does appear to be, however, a difference in incidence of occurrence of major changes in the beta disturbance between electrophoretic patterns of normal serum and of serum of poliomyelitis patients. Whereas in normal serums only 20 per cent of the patterns done in veronal buffer and 65 per cent of the patterns done in phosphate buffer show 2+ or 3+ changes in the beta disturbance, in poliomyelitis serums 50 per cent of the patterns done in veronal buffer and 78.5 per cent of the patterns done in phosphate buffer show similar changes. Statistical evaluation of these data

TABLE III. THE BETA DISTURBANCE IN SERUM SAMPLES FROM NORMAL CHILDREN

BUFFER	NUMER OF SAMPLES	NO CHANGE		1+ CHANGE		2+ CHANGE		3+ CHANGE		PER CENT SHOWING NO OR SLIGHT CHANGE	PER CENT SHOWING MAJOR CHANGE
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT		
Veronal	20	9	45	7	35	2	10	2	10	80	20
Phosphate	20	5	25	2	10	5	25	8	40	35	65

reveals that the differences observed in veronal buffer between normal serums and poliomyelitis serums are statistically significant, while those observed in phosphate buffer are not. However, it appears very likely that if the series were sufficiently expanded these consistent differences would also become statistically significant.

DISCUSSION

The exact cause of the beta disturbance still remains unknown. It was considered by Longsworth and co-workers[3, 4] to be due to convections arising from reactions in the neighborhood of the beta boundary following the electrophoretic separation of the components. In the process of electrophoretic separation there results a situation in which in the descending leg of the electrophoresis cell the beta globulin is migrating in the absence of albumin and alpha globulin, whereas in the ascending leg of the cell it is not. Longsworth and his collaborators suggest that the absence of the albumin and alpha globulin fractions in the beta region in the descending leg of the electrophoresis cell may result in a stability change which permits the convections of which they speak to arise, thus explaining the appearance of a beta disturbance in the descending but not in the ascending electrophoretic pattern.

It has been postulated[5] that this beta disturbance spike, extending indefinitely out of the picture of the descending boundary, corresponds to the presence of a turbidity and that the disturbance is not entirely dependent on a refraction gradient. The turbid material transmits no light and, therefore, the spike is of infinite length. However, the dense layer is not too opaque to transmit light in all cases; in cases in which light is transmitted the spike does not have infinite length, but the pattern simply shows a steep gradient at that point.

There has been considerable difference of opinion concerning the origin of this turbidity. The suggestion has been made[5] that it might be due to an interaction between alpha and gamma globulin. According to Longsworth and his collaborators[3] it may be due to a stability change by removal of other components. Moore points out, however, that, if this were true, it would appear that the entire beta region which is free of albumin and alpha globulin should show turbidity rather than just the narrow region near the slow end of the beta boundary. Abramson, Moyer, and Gorin[5] suggest that there might be two beta globulins of different stabilities, the slower-moving one being more unstable in the absence of the faster-moving one.

Evidence supporting this latter view was brought forward by Chargaff, Ziff, and Moore[6] who demonstrated that the addition of heparin causes disappearance of the beta disturbance. Chargaff[7] suggests that the turbidity is associated with a weak lipoprotein complex existing in the components of the beta globulins which becomes partially dissociated when the beta components are under the influence of an electric field in the absence of the albumin and alpha globulin components of the serum, the situation which exists in the descending leg of the electrophoresis cell.

In agreement with this suggestion there is considerable evidence that the lipids of blood serum are present in the form of lipoprotein complexes of varying degrees of stability. Sørenson[8] first suggested the occurrence of lipoprotein complexes in normal serum because he felt that the perfect clearness of such liquids as serum and plasma in spite of their contents of lipid materials could be explained only by assuming linkage between lipids and proteins. Tiselius[9, 10] noted that most of the lipid material of normal serum and the opalescence of normal serum, due presumably to suspended fat globules, migrate with the beta globulin fraction. Abramson[11] has demonstrated that the mobility of a particle suspended in a protein solution is due to the adsorption of a layer of protein on the surface of the particle and, in general, has the same value as the mobility of the adsorbed protein. Therefore, it seems logical to conclude, as Longsworth[4] has, that the suspended fat particles of serum are coated with a layer of beta globulin.

In electrophoretically separated serum proteins, lipids are present in all fractions with the largest amounts being associated with the beta globulin and alpha globulin fractions, respectively.[12] Kendall[13] demonstrated that even four-times recrystallized human serum albumin contains a certain lipid residuum. Longsworth and MacInnes,[4] working with nephrotic serum, found that high speed centrifugation cleared the serum by removal of fat particles but that cold ether extraction removed still more lipid material as evidenced by significant decreases in the beta globulin fraction. On the other hand, in the case of normal serum little lipid can be extracted by shaking with cold ether but considerably larger amounts can be removed by freezing in the presence of ether.[14] Blix[15] by extracting with cold acetone and Zeldis, Alling, McCoord, and Kulka[16] by extracting with cold alcohol have succeeded in removing the major portion of the cholesterol and a large portion of the phospholipids from the serum proteins. However, Zeldis and his collaborators conclude in agreement with the finding of Kendall[13] that a certain portion of the bound lipids can be freed only by denaturation of their protein components.

It is interesting to note that Zeldis and his collaborators[16] observed regular disappearance of the beta disturbance in samples of serum extracted by cold alcohol whereas Longsworth and MacInnes[4] found persistence of the beta disturbance following extraction with cold ether. This would appear to support the suggestion of Chargaff[7] that the turbidity corresponding to the beta disturbance results from dissociation of a lipoprotein complex when the beta components are under the influence of an electric field in the absence of albumin and alpha globulin. In this connection it should also be noted that the beta disturbance is absent in electrophoretic patterns of nephrotic urine[4] and of spinal fluid.[17] In both of these cases it might be assumed that this lipoprotein complex, representing an entity of large particle size, is selectively removed by the membranes through which these fluids are filtered. Certainly one may say in these cases as well as in the cases of those samples of serum which have patterns with completely absent beta disturbance either that one of the constituents of the complex is missing or that conditions which favor formation of a turbid layer are absent.

Regardless of the exact mechanism involved, it is apparent from our data that in electrophoretic patterns done in phosphate buffer the occurrence of the beta disturbance as a narrow spike of infinite length is much less common and the complete absence of the beta disturbance is much more common than in patterns done in veronal buffer. Longsworth, Shedlovsky, and MacInnes[3] reported that the beta disturbance is almost always observed in the pattern of the descending boundaries. Dole[18] found that fourteen of fifteen normal subjects showed a beta disturbance and the fifteenth showed it on repetition. Furthermore, one subject showed the beta disturbance on nineteen of twenty runs, the one exception being when the blood was not drawn as a fasting sample. In our series of twenty normal children reported here, the beta disturbance is completely absent (3+ change) in 10 per cent of the patterns done in veronal buffer and in 40 per cent of the patterns done in phosphate buffer. It is present as a narrow spike of infinite length (0 change) in 45 per cent of the patterns done in veronal and in only 25 per cent of the patterns done in phosphate buffer.

Thus, it seems apparent that for some obscure reason there is less tendency to form a turbid layer in the beta component of the descending limb of the electrophoresis cell in the presence of phosphate buffer than in the presence of veronal buffer. If one accepts Chargaff's explanation of the beta disturbance, it may then be concluded that the dissociation tendency of the lipoprotein complex whose dissociation produces the turbidity corresponding to the beta disturbance is decreased in phosphate buffer as compared to its dissociation tendency in veronal buffer.

The greater incidence of occurrence of major changes in the beta disturbance in electrophoretic patterns of serum from poliomyelitis patients than in patterns of serum from normal subjects, irrespective of the buffer used, is a definite observation of our present study. In the previous paper[2] it was tentatively suggested that the dissociation tendency of the lipoprotein complex, whose dissociation produces the turbidity corresponding to the beta disturbance, is decreased in patients with poliomyelitis. An alternative explanation which should be considered is that this lipoprotein complex is absent or decreased in concentration in the serum of poliomyelitis patients. Perhaps careful investigation of the lipid constituents of such serums would yield important information in this regard. Until the true nature of the beta disturbance is more clearly understood, no definite conclusions as to the true significance of the changes which occur in patients with poliomyelitis are justified.

SUMMARY AND CONCLUSIONS

1. The patterns obtained in 252 electrophoretic experiments on blood serums of normal children and of poliomyelitis patients have been analyzed with regard to the appearance of the beta disturbance.

2. Marked changes (2+ and 3+ changes) in the beta disturbance were found to occur in the electrophoretic patterns of the serum of normal chil-

dren in 20 per cent of the cases done in veronal buffer and in 65 per cent of the cases done in phosphate buffer.

3. In cases of poliomyelitis similar changes were found to occur in 50 per cent of 142 cases that were studied in veronal buffer and in 78.5 per cent of 70 cases studies in phosphate buffer.

4. No correlation was found to exist between the changes observed in the beta disturbance and the severity or the duration of the disease.

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MYOTONIA CONGENITA

DONALD R. HIRSCH, M.D., JOSEPH DANCIS, M.D., AND RICHARD S. WARD, M.D.
NEW YORK, N. Y.

MYOTONIA congenita is a hereditary condition in which the patient is unable to relax his muscles quickly after a strong voluntary contraction. It is commonly associated with muscular hypertrophy. The condition is usually not disabling and the prognosis for life is good. The disease is rare, but is one of great interest to physiologists because of the possibility that an understanding of the mechanisms behind the muscular abnormality will give us an insight into the physiology of normal muscular contraction.

Myotonia congenita was first described by Bell in 1833. It received general recognition, however, only after Thomsen described twenty-one cases in his own family in 1876. A related disease, dystrophia myotonia, is more common. This latter condition has an onset later in life and there are associated findings: muscular atrophy and weakness, cataracts, testicular atrophy, baldness, and a low basal metabolic rate. Most of the studies on myotonia have been carried out on patients with dystrophia myotonia, but so far as we know the muscular abnormality is the same in the two diseases, varying in severity. There are several good reports and reviews on this subject in the literature.[1-6, 9, 10]

The justification for an additional report lies in the use of two new approaches to the study of myotonia: (1) a search for a humoral substance in the blood of a patient with myotonia, which would be capable of reproducing myotonia, and (2) observation of the effects of curare on the myotonic reaction. The latter of these techniques has become available for clinical research only in the past few years.

CASE REPORT

H. C., a 6-year-old Negro boy (B. H. 28255-47) was admitted to Bellevue Hospital in June, 1947, with a chief compalint of persistent symmetrical swellings in the neck region. It was also reported that the child seemed slow and lethargic in play.

The child came from a boarding school, and only the father was available to give a history. He described the patient's birth and neonatal development as normal, except perhaps for the fact that the child's muscular development had always seemed advanced for his age. Aside from measles, chicken pox, and appendicitis requiring operation, there had been no illnesses. The child had entered the boarding school eight months before the hospital admission and the admitting physician had noted the bilateral neck swellings, which he attributed to cervical lymphadenitis secondary to chronic tonsillitis. In the school, it was noted that the boy walked slowly and seemed sluggish in play, compared to the other children. He was also seen to have a peculiar staring mannerism, most noticeable in the early morning on awakening.

From the Department of Pediatrics, New York University-Bellevue Medical Center and the Children's Medical Service, Bellevue Hospital.

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The father and two brothers of the patient were healthy and free from muscular abnormalities. Both the mother and the maternal grandmother, however, were said to show prominent overdevelopment of the muscles of the neck and shoulder girdle, and to suffer from an inability to move rapidly. The mother had the same staring mannerism as the child.

Physical examination on admission showed an alert, intelligent, well-developed and well-nourished Negro boy of 6 years of age. He was not ill. Positive findings were limited to the skeletal muscle system and the eyes. The tonsils were large and cryptic, but free of active infection. There were no signs of hypothyroidism. Neurologic examination was negative except for the muscle findings.

Fig. 1.

Fig. 2.

Fig. 1.—Obvious lid lag due to increased tonus of the levator palpebrae.

Fig. 2.—The patient has been instructed to close his eyes tightly and then open them as rapidly as possible. The photograph was taken about two seconds after the patient began to open his eyes. The palpebral orifice is still reduced in all diameters despite the maximal effort he is making to open his eyes.

The child's herculean build was striking. The masses in the neck region could be demonstrated to be hypertrophied strenocleido mastoid muscle rather than lymph nodes. The muscles of the shoulder girdle stood out clearly.

The abnormalities in eye movements first suggested to us that the patient was suffering from a generalized muscle disturbance. There was severe myotonia of all the extraocular muscles. The child had great difficulty in following rapidly moving objects with his eyes. If an object were moved vertically or horizontally in front of him, there would be a short interval before he could make his eyes move in the required direction. When he closed his eyes tightly and then tried to open them again, he could not do so for

several seconds, even though he tried hard. He had pronounced lid lag, which we attributed to myotonia of the levator palpebrae superioris. There was no exophthalmos.

These abnormalities of the extraocular muscles were most marked in the early morning on awakening. The myotonia disappeared rapidly when the affected muscles were "warmed up." Thus after the child had opened and closed his eyes several times in succession, the movements became progressively easier, and lid lag disappeared. Aside from these abnormalities of movement, examination of the eyes revealed nothing. This included slit lamp examination.

Fig. 3.—There is marked muscular hypertrophy. The scar is the result of a muscle biopsy.

Myotonia was then found in other muscles, too. After strongly flexing or extending his neck the child had difficulty in straightening it. His gait was abnormally slow and labored. He appeared stiff-jointed. Here the "warming up" phenomenon could be clearly seen; after five or six steps his gait was normal. Myotonia reappeared rapidly if he did not continue to use his muscles.

The myotonia could also be demonstrated after mechanical stimulation of muscle groups. When the thenar eminence of the hand was tapped with a percussion hammer, contraction was rapid and strong, and relaxation delayed. The brachioradial "reflex" was similarly abnormal.

Routine laboratory results were as follows: The routine urinalysis was negative. Blood count showed hemoglobin 14.5 Gm., red blood count 4.27 million, white blood count 5,800, polymorphonuclear leucocytes 28 per cent, lymphocytes 68 per cent. This lymphocytosis persisted on all the examinations. Mazzini test was negative. X-rays of the skull, long bones, neck, lungs, and heart were negative. Carpal and tarsal ossifications were within normal limits. Serum calcium was 10.4 mg. per cent and serum phosphorus 4.5 mg. per cent. Mantoux tests were negative up to 1.0 mg.

Several observations were made on the behavior of the myotonia under a variety of conditions. These experiments were repetitions of experiments previously reported by others in the literature. No attempt was made to record results mechanically or electrically; the evaluation was entirely clinical. Changes that were observed were unequivocal.

1. Electrical reactions: Increased muscle excitability in myotonia had been found previously by Poncher and Woodward.[1] It usually required a galvanic current of 1.8 Ma. to produce a muscular contraction in a normal 6-year-old child. In this patient currents of less than 1.0 Ma. were sufficient.

2. Effects of chilling: It is generally reported that myotonia is worse in cold weather, although Ravin[2, 3] found that myotonia in his patients decreased when the temperature of the environment was reduced from 40° C. to 20° C. Our patient was placed in a cold bath for about ten minutes. He was then moved out into the open air. At this time the myotonia was unchanged, despite the fact that he was shivering with cold.

3. Epinephrine: In the literature there are conflicting reports as to the effect of epinephrine on myotonia. Some investigators report accentuation of symptoms,[1, 4] and others a decrease.[2, 3] In our patient repeated injections of 0.3 c.c. of 1:1000 epinephrine hydrochloride intramuscularly had no effect on the myotonia.

4. Prostigmine: There is a uniformity of opinion that prostigmine accentuates myotonia.[4-7] The injection of 1.0 c.c. of 1:2000 prostigmine hydrochloride intramuscularly exaggerated the myotonia in our patient.

5. Quinine: Since 1936,[4, 6, 8] quinine has been used as a specific medication in this disease. Small doses often cause a complete disappearance of the myotonia. Our patient was completely relieved of his symptoms by 0.6 Gm. quinine sulfate orally, or 0.5 Gm. quinine dihydrochloride intravenously. The myotonia returned slowly in six hours.

6. Dual nature of the myotonia contraction: This feature of myotonia was commented on by Dana[9] and Griffith,[10] and has more recently been investigated by Ravin.[2] The myotonia contraction appears to be initiated by the first strong voluntary contractions, but from then on is independent of them, lasting a definite period regardless of whether relaxation is attempted following these first contractions, or whether a voluntary tetanus is kept up.

The boy was asked to close his eyes tightly for varying lengths of time, after which he was to open his eyes as quickly and as widely as possible. The length of time it took him to open his eyes was recorded. It was found that a minimum period of voluntary contraction was necessary (two seconds) before myotonia appeared. Beyond that minimal period, however, the duration of myotonia was not increased by having the boy squeeze his eyes shut for longer periods. On the contrary it took him less time to open his eyes the longer he kept them closed. When he kept them closed for ten seconds no myotonia was noted on relaxing. This can be interpreted as meaning that the myotonia ran its course under cover of the prolonged voluntary effect.

In summary, a 6-year-old Negro boy presented the classical picture of myotonia congenita. He had pronounced hypertrophy of many of his skeletal muscles, and an inability to relax antagonistic muscles rapidly. Rapid movements thus could not be accomplished. The myotonic delay in relaxation disappeared after several "warming up" contractions. The family history suggested that both the patient's mother and the maternal grandmother suffered from the disease. Observations of the myotonic reaction in this boy, under varying conditions, were consistent with similar observations on cases previously reported in the literature.

SPECIAL STUDIES

A. *Search for a Humoral Factor.*—The drug veratrine can produce myotonia in normal muscle. An isolated strip of muscles, poisoned with veratrine, behaves remarkably like the muscle of myotonia congenita.[11] There is a myotonic pattern of response following stimulation of the nerve. If electromyograms are made from the muscle during the myotonic contraction, it is found that a single shock stimulus in the nerve produces a volley of electrical impulses in the muscle. The veratrine reaction disappears following repeated contraction, or "warming up." Quinine also abolishes the reaction. In all these cardinal points the myotonia of veratrine poisoning resembles that of myotonia congenita. Even in response to curare poisoning the two types of myotonia behave similarly. Curare affects neither (see section B).

In view of this, it seemed reasonable to search for a veratrine-like substance in the blood of patients with myotonia. In 1936 Loewi[12] reported success in finding such a substance in the plasma dialysate of a patient with myotonia congenita. His experiment needed to be repeated. Using essentially the same technique, we attempted this with our patient. The procedure was as follows:

Blood from the external jugular vein was used, because of the prominence of eye signs in this patient. Specimens were also taken from the antecubital vein, before and after tourniquets had been applied. The blood was drawn, heparinized, separated, and frozen until ready for testing. Control specimens were obtained under identical conditions from a normal child. The sartorius muscle of a frog was exposed to (1) the dialysate, and (2) the residue, and was stimulated each time with a galvanic current. The sartorius muscle is usually used for such testing. Characteristic patterns are produced by veratrine in dilutions as high as 1:5,000,000.

No veratrine-like substance could be detected in any of these specimens. A normal twitch resulted in each case.*

An in vivo experiment was also tried with this patient, in the hope of demonstrating a myotonia-inducing substance in the blood. The idea for this experiment was taken from the classical one on myasthenia gravis described by Mary B. Walker before the Royal Society of Medicine in 1938.[13]

Tourniquets were placed on the child's arms to obstruct venous return. This was to increase the concentration of such a substance locally. The patient was instructed to open and close his eyes repeatedly until his eye muscles had "warmed up," and all signs of myotonia disappeared. At this point he was asked to open and close his hands several times. Myotonia of the hands was quite evident. The tourniquets were then abruptly removed. It was thought that with the release of this venous blood into the general circulation a myotonia-inducing substance might cause the myotonia of the eye muscles to reappear. No such effect resulted.

We were not able to demonstrate a humoral factor by this in vivo experiment.

B. *Curarization Experiment.*†—In recent years investigators have come to

*We are indebted to Dr. Givlio Cantoni for performing these experiments.
†Dr. Emmanuel Papper supervised the curarization in these experiments.

the conclusion that the site of the abnormality in myotonia is peripheral. However, the exact locus is not known. Kennedy and Wolff[4] demonstrated that spinal anesthesia does not affect myotonia. Schaffer[13] showed that myotonia persisted when the nerve endings in the muscles were paralyzed by regional anesthesia. Brown and Harvey[7] showed that section of the motor nerves and degeneration of the motor end plate did not alter the abnormality. This last work was done with myotonic goats—goats with a congenital disease resembling human myotonia congenita.

Curare is a logical drug to use in carrying this localization further. Curare is said to paralyze muscle through action on the myoneural junction. In an excellent review of the literature, McIntyre[14] pointed out that the chief effect of curarization was a diminution in the end plate potential. Apparently there was also some effect upon the muscle fibers themselves, diminishing their sensitivity to acetyl choline, but this need not concern us. All effects of curare are either upon the myoneural junction or on points distal to it.

In 1939 Brown and Harvey[7] curarized myotonic goats and found the myotonia uninfluenced by the curare. They reasoned from this experiment that the site of the abnormality in the goats was peripheral to the myoneural junction. There have been no reports of this experiment carried out with a human case of myotonia. Accordingly, with our patient, the following procedure was undertaken:

The patient received nembutal and scopolamine premedication, and was anesthetized with vinyl ether and ether-oxygen mixture. The response after mechanical stimulation of the extensors of the forearm (the brachioradial "reflex"*) was used as an index of myotonia. Motion pictures were taken of all reflexes elicited. After pictures were taken of the "reflex" before curare, curare was given until diaphragmatic contractions stopped.† A total of 30 units was used. Respirations were maintained by the anesthetist. Pictures were then taken of the "reflex" under the influence of curare.

We were fortunate to be able to make control observations on a normal child of the same age and weight under identical conditions of anesthesia. Here, too, motion pictures were taken of the brachioradial "reflex" before and after full curarization.

Mechanical stimulation of the extensor muscles of this boy's forearm produced (under anesthesia) a strong contraction with a myotonic delay in relaxation; the hand remained up for several seconds, and only fell slowly to its original position. After complete curarization this response was unchanged. In the normal control the normal brachioradial "reflex" was also uninfluenced by curare.

*The brachioradial "reflex" is not a true reflex in the strict sense of the word. It does not depend upon a reflex arc, and is independent of the central nervous system. It is apparently a direct response to mechanical stimulation of the muscle fibers themselves. The persistence of the reflex after curarization makes this apparent. We have been unable to find any comment on the myotatic nature of this reflex in the literature, although it appears to be generally accepted by neurologists.

†This degree of curarization is commonly accepted as complete since the diaphragm is the last muscle to be paralyzed.

In human beings with myotonia congenita, therefore, as well as in myotonic goats, curare does not eliminate the myotonic reaction. The abnormality in myotonia must then be peripheral to the site of action of curare. Since, according to our present knowledge, all effects of curare are at the myoneural junction or distal to it, this would put the abnormality in human myotonia somewhere in the muscle fiber itself.

SUMMARY

1. The clinical findings in a case of myotonia congenita (Thomsen's disease) are presented.

2. Attempts at demonstrating a myotonia-inducing substance in the blood of the patient are described. These attempts were unsuccessful.

3. The myotonic pattern of response was uninfluenced by complete curarization of the patient. The significance of this in the localization of the muscular abnormality is discussed.

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Case Reports

POLYOSTOTIC FIBROUS DYSPLASIA

LOUIS J. HACKETT, JR., M.D., ALBANY, N. Y., AND
WILLIAM M. CHRISTOPHERSON, M.D., NEW YORK, N. Y.

IN 1937 Albright, Butler, Hampton, and Smith[1] described a syndrome characterized by the presence of multiple bone lesions, areas of skin pigmentation, and, in the female, precocious puberty. The term osteitis fibrosa disseminata was suggested to differentiate this entity from osteitis fibrosa generalisata of hyperparathyroidism. Lichtenstein,[2] in 1938, suggested the entity be designated polyostotic fibrous dysplasia. Since that time, authors[3-10] have used various names to designate the condition; of these, Albright's syndrome seems to be the most popular. This would seem fitting because Albright has contributed most to the correlation of the triad, even though isolated cases were reported as early as 1922 by Weil.[11] However, Albright[12] suggests that Lichtenstein's term polyostotic fibrous dysplasia be accepted as preferable.

The case reported is a classical example of the complete syndrome of polyostotic fibrous dysplasia, interesting for the unusually early manifestations of precocity.

CASE REPORT

A 5-year-old white female was seen in the pediatric clinic of the Louisville General Hospital on Oct. 28, 1948, with a mild upper respiratory infection. It was evident that her physical development was considerably advanced for her chronological age. Her breasts were prominent and there was a moderate growth of pubic hair. The mother stated that the precocious development had not been a cause of alarm since the child had menstruated on the second day of life and a three-day menstual period had recurred at regular twenty-eight day intervals since the onset. The breasts were prominent at birth and had steadily enlarged. Four siblings were in good health. The patient was four inches taller than a brother one year older. The child had never been severely ill, was always quiet, bashful and "very nervous," and rarely played with other children.

She walked with a marked limp. There was a swollen ecchymotic area over the anterior aspect of the middle third of the left tibia which had been present for two weeks; it was tender and slightly warm.

There were several areas of dark brown pigmetation over the right half of the trunk. The largest area was on the back; it was not elevated, had an irregular sharply demarcated border, and measured 11 cm. in greatest diameter. Similar, but smaller, areas of pigmentation were noted on the buttock, side, abdomen, and chest. There were no cutaneous or subcutaneous tumors. No areas of pigmentation were found in the mouth. The breasts were adolescent with prominent areolae.

Laboratory Data.—Red blood count was 4.85 million, hemoglobin 80 per cent, white blood count 10,200, polymorphonuclear leucocytes 31 per cent, lymphocytes 64 per cent, monocytes 5 per cent. Urinalysis was normal. Nonprotein nitrogen was 27 mg. per 100 c.c., calcium 11.2 mg. per 100 c.c., phosphorus 4.8 mg. per 100 c.c., alkaline phosphatase 8.4 Bodansky units, serum albumin 5 Gm. per 100 c.c., serum globulin, 2.4 Gm. per 100 c.c.

From the Departments of Pediatrics and Pathology, University of Louisville School of Medicine, Louisville, Ky.

X-ray examination of the skeleton showed multiple areas of "cystlike" lesions involving the humerus, ulna, metacarpals, phalanges, ilium, femur, tibia, and fibula on the left and the femur and fibula on the right (Figs. 1 and 2). The lesions were chiefly hypo-ostotic with only a few hyperostotic areas. There was

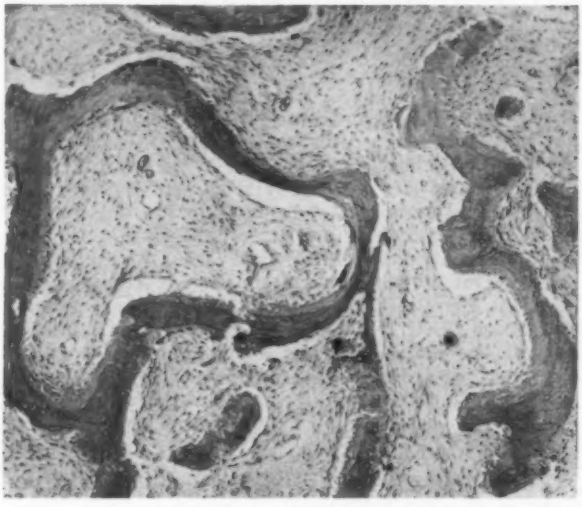

Fig. 1.—Section through medullary canal of left fibula. (×120.)

Fig. 2.—Irregular area of pigmentation resembling the coast of Maine.

considerable thinning of the cortex in the left tibia, femur, and fibula, with expansion of the fibula. There was a pathologic fracture of the middle third of the left tibia. The epiphyses were not involved and there was no osteoporosis.

A segment of the left fibula was obtained for pathologic examination. The cortex was thinned and the medullary canal was replaced by gritty gray fibrous tissue. Microscopically, the thinned cortex had rather wide Haversian canals which contained fibrous tissue rich in thin-walled vessels. The normal architecture of the medullary canal was completely distorted. Numerous thin poorly-organized septa of new bone with a peripheral zone of osteoid were surrounded by rather cellular mature fibrous connective tissue containing very few thin-walled vascular channels. There were a few collections of osteoclasts at the periphery, and some osteoclastic resorption of the new bone and osteoid tissue. The sections were typical of fibrous dysplasia.

Fig. 3.

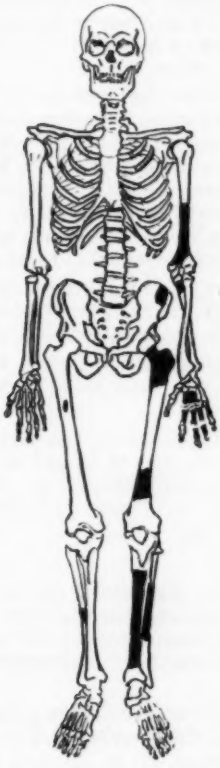

Fig. 4.

Fig. 3.—Lateral view of left tibia and fibula. Pathologic fracture can be seen.
Fig. 4.—Schematic distribution of bone lesions, predominantly on the left.

COMMENT

Such a triad of seemingly dissociated manifestations as are presented in the above case makes the diagnosis of polyostotic fibrous dysplasia one of the more easily recognized syndromes. The differential diagnosis involves consideration of neurofibromatosis, hyperparathyroidism, Ollier's dyschondroplasia,

and xanthomatosis. Since in none of the above conditions do we have similar clinical, radiographic, or pathologic findings, it would seem unlikely that there would be much confusion. However, from the number of patients with indisputable polyostotic fibrous dysplasia who have been subjected to parathyroidectomy,[4] it appears that the distinction, however easy, is not always made.

Perhaps the most easily confused disease is neurofibromatosis with bone involvement and cutaneous pigmentation. In neurofibromatosis Albright[12] points out that the pigmented areas are shaped like the coast of California rather than the coast of Maine (Fig. 2). In addition, there are usually multiple cutaneous neurofibromata. The bone lesions are relatively few, commonly involving the lower end of the femur and upper end of the tibia, and there are sharply circumscribed areas of distruction with very little, if any, evidence of new bone formation. In polyostotic fibrous dysplasia, on the other hand, there are extensive bone lesions in which overgrowth of bone, as well as bone destruction, is a prominent feature.

Hyperparathyroidism is rare in children, seldom runs such a slow course, and is accompanied by alterations of the serum calcium and phosphorus. Pigmentation and precocious puberty are, of course, lacking; and, finally, the bone lesions are quite different. The bone lesions in fibrous dysplasia have a tendency to be unilateral; the epiphyses are rarely, if ever, involved. Parts of the skeleton appear normal. There are both hyperostotic and hypo-ostotic lesions and there is no osteomalacia. Precocious bone age may be present. Finally, a well-chosen biopsy of the bone will confirm the diagnosis.

Radiographic examination, plus the history and physical examination, with biopsy, if necessary, should clearly differentiate polyostotic fibrous dysplasia from Ollier's dyschondroplasia, and xanthomatosis of bone.

Skin pigmentation is often proportional to the bone involvement and is said to occur on the same side;[8] however, this is not constant, as indicated in the case reported.

The pathogenesis of the precocity remains unexplained, although the theory that it may be due to lesions in the walls of the third ventricle and the hypothalamus[5] remains attractive. The autopsy in Albright's Case 3 revealed no evidence that ovulation had ever occurred. Sternberg and Joseph[9] reported similar findings.

SUMMARY

A case of polyostotic fibrous dysplasia in a 5-year-old girl is reported.

The diagnosis was made by the characteristic triad of predominantly unilateral bone lesions, precocious "puberty," and unilateral skin pigmentation, and was substantiated by radiographic and pathologic examination of the bone lesions.

The early onset of menses (second day of life) is somewhat unusual as is the contralateral distribution of skin pigmentation.

The differential diagnosis is discussed briefly.

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CONGENITAL ATRESIA OF THE INTESTINE IN A PREMATURE INFANT

BEULAH M. KITTRELL, M.D., LEA CALLAWAY, M.D., AND LYNN F. CURTIS, M.D.
MARYVILLE, TENN.

CONGENITAL atresia of the gastrointestinal tract is an extremely rare anomaly occurring, according to most estimates, about once in twenty thousand births. Arnheim[1] tabulated the results of infants treated surgically and reported in the literature from 1911 to 1943. These cases were in infants ranging in age from one hour to 8 days. All were treated by primary anastomosis. Miller[2] stated that primary anastomosis is the surgical procedure of choice and that primary ileostomy offered absolutely no chance for recovery. That this attitude is well established as authoritative is borne out by a cursory review of the literature.

Erb and Smith[3] reported two cases, one with multiple atresias treated by primary anastomosis. Miller, Greengaard, Raycroft, and McFadden also reported successful treatment of two cases in this manner. Duncan, Wearn, Jackson, and Waldron[5] successfully treated multiple atresias in a premature infant by short-circuiting anastomosis. Ficcara and Degen[6] reported a patient who died of meconium peritonitis after operation.

James R. Judd[7] reported the first successful case cured by ileostomy alone. A full-term Chinese female infant showed signs of intestinal obstruction following the first feeding. Surgery was done in four stages. Supportive measures in the form of blood, vitamins, antibiotics, and parenteral fluids were vigorously employed. This case finds a close parallel in the following report in a premature infant treated successfully by primary ileostomy.

CASE REPORT

The child, a female, born at seven and one-half months' gestation, weighed 4 pounds at birth. She was apparently normal except for prematurity and bilateral coloboma.

Immediately after delivery she was placed in an incubator and given continuous oxygen. There was considerable mucus from the posterior pharynx and fluids were withheld until the fourteenth hour, at which time weak tea was given by dropper and continued thereafter every two hours. Some of the feedings were regurgitated but there was no note of actual vomiting. Early on the second morning while the cord dressing was being changed it was noted for the first time that the child's abdomen was greatly distended. She quickly became cyanotic and the pulse was rapid and feeble. X-ray films (Figs. 1 and 2) showed a marked pneumoperitoneum with no air in the large bowel. A diagnosis of perforated viscus was made and immediate exploration was advised. During the subsequent two and one-half hours while awaiting the sacrament of baptism, lactate Ringer's solution was administered subcutaneously and a gastric lavage was performed. Preoperative medication consisted of phenobarbital 1/4 gr. and atropine 1/2500 gr. given subcutaneously.

Before taking the patient to surgery a No. 20 needle was inserted into the peritoneal cavity to evacuate the gas which was under such pressure as to severely restrict the motion of the diaphragm. This procedure afforded considerable relief of the respiratory distress, although the child remained cyanotic. Because of the poor condition of the patient the only anesthetic used was novocain 1/2 per cent supplemented by a sugar teat dipped in bourbon. In view of the fact that it had been impossible to insert a thermometer into the rectum it

From the Departments of Pediatrics, Surgery, and Obstetrics of the Blount Memorial Hospital.

seemed obvious that we were dealing with a congenital anomaly of the rectum. For this reason it was decided to explore the abdomen through a left rectus incision.

A moderate amount of gas escaped when the peritoneal cavity was opened. A fibrous band was found compressing the terminal ileum approximately two inches from the ileocecal valve. Proximal to this point at which the intestine

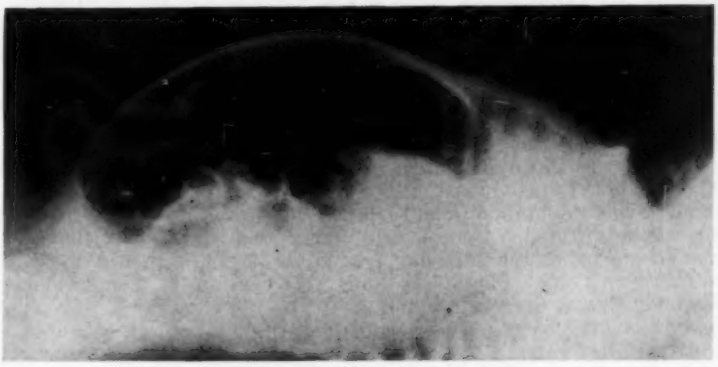

Fig. 1.—Left lateral decubitus.

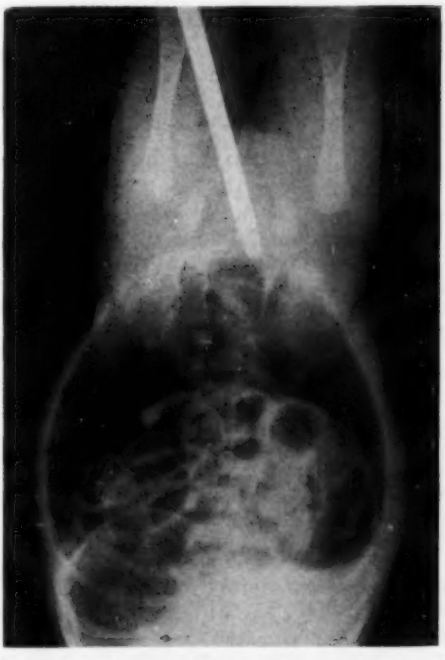

Fig. 2.—Patient inverted. Inability to insert a thermometer for any distance brought up the question of an imperforate anus. In retrospect it would seem that the cause was due to the tremendous intra-abdominal pressure.

was completely severed, the wall of the bowel was very thin and dilated to a diameter of 3 to 3.5 cm. Distal to the constriction band, the ileum was but a fibrous strand of tissue joining a completely empty cecum, which, like the descending colon, resembled a twisted cord approximately 0.5 cm. in diameter. The gravity of the patient's condition and the very atretic appearance of the colon discouraged further surgery at this time. The dilated end of the ileum was brought out through the lower end of the incision, the peritoneum being closed with continuous catgut and the fascia with interrupted cotton sutures.

The infant was returned to the incubator and continuous oxygen was resumed. Amigen solution with dextrose 5 per cent was given alternately with lactate Ringer's solution subcutaneously every six hours. Breast milk and skimmed lactic acid milk of equal parts were started after three hours by dropper feedings. An occasional feeding was vomited during the first thirty-six hours but there was very little abdominal distention at any time. On the third day the child was able to take breast milk from a Breck feeder. After the first week breast milk was unobtainable and Olac, a dried milk mixture of high protein content, was substituted. Ascorbic acid, hypodermatically, and oleum percomorpheum were started on the third day, iron in the form of copperin in the formula on the fourteenth day. Parenteral fluids were continued. The discharge from the ileostomy was at first watery and green; by the fifth day it was yellow and gradually becoming pasty. The weight dropped to 3 pounds, 6 ounces, but by the third week had risen to 3 pounds, 9 ounces. At this time the baby was taking formula well and the stools through the ileostomy were normal.

The situation looked pretty hopeless and at the request of the family the baby was discharged to go home in an incubator and be cared for by an aunt who is a graduate nurse. If and when she attained the weight of 7 or 8 pounds it was planned to do x-ray studies to determine the status of the large bowel. The child began to fail as soon as parenteral fluids were stopped. Her weight again dropped to 3 pounds, 6 ounces and remained stationary. Numerous formulas were tried but Olac seemed the most satisfactory. Dehydration was extreme although the average fluid intake was 5 oz. per pound of body weight. The skin surrounding the ileostomy became red and irritated. After three weeks at home she was readmitted to the hospital, a classic picture of marasmus and dehydration.

With the resumption of parenteral fluids the child's general condition began to improve and soon the weight had increased to 5 pounds at which level it became fixed. During this period it was found that the colon could be filled with barium to beyond the hepatic flexure and that the diameter of the bowel was about the size of a lead pencil. Although still a poor risk it was obvious that there would be no further improvement until she was given the benefit of the absorptive surface of the large bowel. The second operation was done at the age of 3½ months.

Through a right rectus incision the fibrous band which represented the terminal ileum was resected with the appendix and the cecum. The ileostomy was freed from the left rectus wound and together with the ascending colon was fixed in the right rectus incision making a double-barreled ileocolostomy after the manner described by Mikulicz. On the third day a clamp was applied to the spur and the process of diverting the fecal stream into the colon was instituted.

The postoperative course was stormy for the first five days, the temperature ranging between 101° and 106° F. The patient was given penicillin in oil daily and sulfadiazine by mouth. Parenteral fluids were continued. On the fifth day there were yellowish green stools from the rectum, but the spill-over from the ileum into the colon was very disappointing, the major portion being discharged onto the abdominal wall. Two weeks after the second operation

it was necessary to restore about four inches of prolapsed ileum to the abdominal cavity. This was done without opening the abdomen by using interrupted cotton to suture the serosa of the ileum to the skin and fascia.

Continued failure to divert the fecal stream into the colon made the closure of the ileocolostomy quite imperative. The first attempt at closure, using interrupted cotton sutures in the fascia, resulted in the same "ignominious failure" described by Dr. Judd. One redeeming feature in the effort was that although the defect was not closed there was no more protrusion of the ileum.

Three weeks later, after daily rectal dilatations and colonic irrigations, a second and successful closure was made. The child at this time was 4½ months of age and weighed 4 pounds, 8 ounces. The usual technique of inverting the intestinal mucosa of the spur with continuous catgut suture reinforced with interrupted cotton sutures was employed. The fascia was again closed with interrupted cotton sutures. The skin was not closed.

The postoperative course was uncomplicated. Stools became normal, parenteral fluids were no longer required, and the child began to gain weight. She was discharged at the age of 5½ months weighing 6 pounds (a gain of 1½ pounds since final closure of the stoma) and was 20 inches long. At the time she was taking evaporated milk, fruits, vegetables, egg yolk, and strained beef.

In addition to the stormy course described, during her hospital stay she had two upper respiratory infections and one bout of pyelitis. The one blood transfusion was given with the greatest difficulty, the veins being no larger than a small pin. The remarkable fact that the lowest blood value obtained showed a red cell count of 3.5 million and 12 Gm. hemoglobin constitutes a tribute to the possibilities of parenteral feeding.

Her subsequent growth and development since discharge from the hospital have been most gratifying. At 7½ months she weighed 9 pounds 12 ounces and was 22½ inches long (a gain of 3 pounds, 9 ounces in two months). At one year of age she weighed 15 pounds and was 25½ inches long. Her tissue turgor was good, she turned from side to side and supported the weight of her body on her palms. Mentally she seemed alert and responsive.

SUMMARY AND CONCLUSIONS

We have presented a case report of atresia of the ileum with rupture and pneumoperitoneum in a premature infant treated successfully by primary ileostomy.

In retrospect it is felt that more careful attention to the colon and its patency contributed largely to the success of the second closure and might have rendered the first successful. While resection and primary anastomosis is the method of choice, this case proves that failure to carry out such a procedure does not preclude the possibility of a successful outcome.

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Medical Progress

MALIGNANT NEOPLASMS IN EARLY LIFE

JAMES B. AREY, M.D.
PHILADELPHIA, PA.

THE decline in death rates from infectious diseases, coupled with more accurate diagnoses, has resulted in cancer assuming a progressively more important place as a cause of death in infancy and childhood. In the age group one to 14, cancer, including leucemia and Hodgkin's disease, is now the second-ranking cause of death from disease, and in the age group of 5 to 9 years it accounts for more deaths than any other disease.[1] In Massachusetts in 1939, deaths from cancer in children under 15 years of age exceeded those from pertussis, pulmonary tuberculosis, measles, meningitis, scarlet fever, or diabetes, and almost equaled those from pulmonary tuberculosis, meningitis, and scarlet fever combined.[2] In New York in the period 1942 to 1944, deaths from neoplastic diseases during childhood exceeded those from all forms of tuberculosis.[3] The purpose of the present paper is to point out some of the differences between malignant tumors in early life and those seen in the older age groups, and to review some of the features of the more common malignant neoplasms of infants and children.

The infrequency of carcinomas and the high incidence of sarcomas in early life is striking.[4, 5, 6] Pack and LeFevre[5] found sarcoma twenty-two times as frequent as carcinoma in young people less than 25 years of age, whereas if all ages were included, the incidence of carcinoma was almost nine times that of sarcoma.

The malignant neoplasms of early life are frequently radiosensitive, although not, as a rule, radiocurable. In general, they tend to progress rapidly, metastasize widely, promptly recur, and carry a high mortality. Part of the poor prognosis of such tumors, however, is dependent upon ignorance of the physicians and laity as to the occurrence of malignant growths in early life, and is further enhanced by the unfounded assumption that malignant tumors in early life are invariably fatal. Certainly, when compared to the low five-year survival rates of such malignant tumors of adults as carcinoma of the stomach (5 per cent)[7] and carcinoma of the prostrate, the prognosis of many malignant neoplasms of infants and children is actually encouraging. Thus Farber[8] has reported ten of forty patients with neuroblastoma alive from three to eight years after histologic verification of the tumor, and Ladd and White[9] report

From St. Christopher's Hospital for Children, and the Departments of Pediatrics and Pathology, Temple University School of Medicine.

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fourteen of sixty patients (23 per cent) with Wilms' tumor alive two to twenty years after treatment. Although such figures are at variance with many of those in the literature, they do indicate that a defeatist attitude when dealing with such neoplasms is not justified.

Certain malignant tumors are found almost entirely in patients in the younger age groups, as medulloblastoma, Wilms' tumor or embryoma of the kidney, retinoblastoma, and neuroblastoma. Others, such as malignant tumors of bone, soft tissues, blood-forming organs, and tumors of the brain, although also occurring in later life, comprise an important part of the malignant tumors of early life. Although tumors have been described in practically all organs of the body at early ages,[2] the sites most frequently affected by cancer in childhood are the kidneys, the eyes and orbit, the lymphatic and blood-forming organs, the bones, the soft somatic tissues, and the nervous system.[3] The tumors occurring in these sites will now be dealt with in more detail.

Wilms' tumor or embryoma of the kidney is one of the commonest abdominal tumors of childhood.[10] It is a tumor peculiar to infancy and childhood, the great majority of these neoplasms appearing in the first three years of life.[11, 12] The presenting complaint is usually that of an abdominal mass. Fever is present in a significant number of these patients, and a definitely elevated blood pressure may be noted. Hematuria and symptoms referable to the genitourinary tract are far less common than is the case in carcinomas of the renal cortex of adults.

Physical examination reveals a firm, smooth or nodular, nontender mass which may practically fill the entire abdomen. Pyelography reveals distortion of the renal pelvis and calices, displacement of the kidney, and in some instances failure of visualization of the pelvis of the involved kidney. Although pyelograms may be of aid in the differential diagnosis of Wilms' tumor, their greatest importance is in establishing the presence and normality of the opposite kidney, thus preventing the removal of a solitary kidney.

The differential diagnosis includes neuroblastoma of the adrenal, hydronephrosis, mesenteric cyst, and retroperitoneal sarcoma. Although an accurate and correct preoperative diagnosis does much to bolster the ego of the attending physician, attempts to arrive at such a diagnosis should occupy a minimum of time, and repeated, vigorous, and rough palpation of the tumor must be avoided. Final diagnosis must depend upon histologic examination of the tumor, and undue delay in the removal of the tumor in order to arrive at an exact clinical diagnosis should not be condoned.

Grossly, the majority of Wilms' tumors are large, bulky neoplasms which may arise from any portion of the kidney. Nearly all exhibit some degree of encapsulation, the adjoining compressed renal parenchyma often being stretched as a thin layer over the surface of the neoplasm. The cut surfaces are variegated and extensive hemorrhage and necrosis within the tumor may account for the rapid enlargement or sudden appearance of these neoplasms sometimes noted clinically. Involvement of the regional lymph nodes, renal vein, renal pelvis, and ureter should be carefully sought for in order to effect complete removal of the neoplasm.

Histologically, the neoplasm consists of a stroma of loosely or closely packed spindle cells and dark-staining epithelial-like cells having a tubular ar-

rangement; transitions between the epithelial elements and the stromal elements can be demonstrated and strongly suggest a common cell of origin.[10] Glomerularlike structures are sometimes observed. In addition to the above elements, which call to mind the appearance of the embryonic kidney, other "metaplastic" tissues such as smooth and striated muscle, squamous epithelium, and even cartilage may be present.

The treatment of Wilms' tumor consists of nephrectomy plus roentgen therapy. These tumors are radiosensitive, and if the tumor is so large as to make surgical removal unduly hazardous, a preoperative course of irradiation may be used, extending over a period of two to three weeks[10, 13] followed by nephrectomy and postoperative irradiation.

Although the prognosis of Wilms' tumors is very grave, recent reports have been encouraging. Thus Ladd and White,[9] in 1941, report that in general these tumors carry a mortality of from 90 to 100 per cent, yet they report a series of 14 of 60 patients (23 per cent) with Wilms' tumors living and well 2 to 20 years after treatment. As recurrences or metastases, if they are to occur, usually do so within two years following nephrectomy, these 14 patients can be considered as probably cured. Nesbit and Adams[13] report 8 of 16 patients living 3½ to 11½ years after treatment, and Silver[14] reports 10 of 13 patients alive from 2¼ to at least 15 years after nephrectomy. One of these patients developed pulmonary metastases 7 months after nephrectomy, for which he received roentgen irradiation to the involved area with rapid disappearance of the lesions; he is alive and well more than 2 years later with no evidence of recurrence. Dickey[11] reports 4 of 12 patients alive 4 to 15 years after treatment. Certainly results such as those described above, although still indicative of a very grave prognosis, do not warrant a hopeless outlook with respect to these neoplasms.

The neoplasm probably most frequently confused with Wilms' tumor is the neuroblastoma. These tumors are derived from neuroblasts which have migrated from the neural crest to form the adrenal medulla and the sympathetic ganglia. Thus the neuroblastoma, although commonly arising in the adrenal medulla, may also arise from any of a number of other sites, as the cervical ganglia, the region of the bifurcation of the aorta, and the posterior mediastinum.

These tumors are among the most common malignant neoplasms of infants and children, and may be present at birth.[15] They are usually unilateral, but may involve both adrenal glands. The presenting complain may be that of an abdominal mass or may be referable to the presence of metastases, e.g., in the orbits, bone, or cervical lymph nodes. Skeletal metastases are frequently bilaterally symmetrical and may be found in any part of the skeletal system with the exception of the metacarpal and metatarsal bones and the phalanges.[16]

Histologically these neoplasms exhibit varying degrees of differentiation of their neuroblastomatous elements. Thus the more undifferentiated tumors, often referred to as sympathogoniomas, consist of small, round, dark-staining cells with little or no cytoplasm, no fibrillar differentiation, and no pseudorosettes. Somewhat more differentiated tumors, sympathicoblastomas, show the more classical appearance, with many of the cells being arranged in rosettelike

clusters, surrounding a central nonnucleated fibrillar zone made up of fibrils derived from the surrounding cells; no actual lumen is present within these pseudo-rosettes, thus distinguishing them from the true rosettes of the retinoblastoma. Still other more differentiated tumors may show well-differentiated ganglion cells and nerve fibers. Multiple sections may be necessary in order to establish the neurogenic nature of these tumors, and in the past many of them have been referred to as round-cell sarcomas or lymphosarcomas.[17]

The treatment of neuroblastoma consists of surgical removal of the primary tumor followed by irradiation. Even in the presence of local metastases, as to the liver, the prognosis is not hopeless and radiation treatment should be tried even when metastases to bone are present.[16] Untreated, the outcome is almost invariably fatal within a few months after the onset of symptoms,[18] although isolated examples of spontaneous maturation of a malignant neuroblastoma into a benign ganglioneuroma have been reported.[19] Farber[8] has further pointed out that the neuroblastoma may undergo spontaneous hemorrhage and necrosis and disappear without any treatment.

Although an almost hopeless prognosis of neuroblastoma is reported by the majority of authors,[18, 20] Farber[8] reports 10 of 40 patients alive from three to eight years after operative discovery and histologic verification of such tumors. Again, as in the case of Wilms' tumor, the prognosis, although very grave, warrants every attempt to effect a cure of these patients.

Retinoblastoma is a rare tumor, occurring only once in about every 34,000 living births.[21] It is seen almost exclusively in infancy and early childhood, and may be present at birth; from 20 to 30 per cent are bilateral.[22] A strong hereditary tendency to the disease has been observed, although the majority of examples observed clinically appear to be sporadic.[21] However, there is evidence to indicate a probable relationship between the sporadic and the familial types of the disease, so that "sterilization of any child who survives enucleation or irradiation for retinoblastoma and the interdiction of further progeny to the parents of a child with retinoblastoma appear to be justifiable measures."[21]

These tumors are usually first recognized by the presence of a peculiar pupillary reflex, the amaurotic cat's eye reflex, although this may be preceded by dilation of the pupil of the involved eye.[23] Involvement of the opposite eye may be demonstrable at the time of the initial examination or may not become evident for several months, or, rarely, several years. Bilateral involvement is thought to represent multiple primary growths rather than metastatic growth.[21, 24]

Histologically these tumors consist of small dark-staining cells often collected about blood vessels, with extensive intervening necrosis. Areas of calcification may be present. The most characteristic feature, not present in all tumors nor always present uniformly throughout a given tumor, is the presence of true rosettes. These consist of columnar cells arranged about a central cavity, with their nuclei located at the basilar portion of the rosette. These rosettes are thought to represent developing rods and cones.[25]

The treatment of retinoblastoma consists of enucleation of the involved eye with removal of as large a portion of the nerve as possible.[22] The opposite eye

must be carefully observed for the development of tumor. In the presence of bilateral tumors, when vision remains in one eye treatment may consist of surgical removal of the eye with the more advanced disease and fractionated irradiation of the opposite eye, in an attempt to conserve vision. Using such treatment Martin and Reese[24] were able to report two of eight patients living, without recurrence and with vision five years later, and four of the eight patients living without recurrence but blind five years later.

Although intracranial tumors are less frequent in infants and children than in adults,[26] they comprise an important group of neoplasms in childhood. Tumors of the central nervous system comprised 44 per cent of 750 cases of malignant disease of children less than 15 years of age observed at the Mayo Clinic between 1921 and 1930.[4] Tumors of the brain and central nervous system ranked third as a cause of death from malignant disease at ages one to 4 years and second at the age periods 5 to 9 years and 10 to 14 years, according to figures obtained from children insured in the Industrial Department of the Metropolitan Life Insurance Company, from 1943 to 1947.[1]

Intracranial neoplasms occurring in infancy and childhood are preponderantly gliomas, and the majority are infratentorial in location. Thus Keith, Craig, and Kernohan[27] found that gliomas constituted 84 per cent of the intracranial neoplasms in children; 66 per cent of all tumors were infratentorial and 34 per cent were supratentorial.

The most constant and one of the most important symptoms of an intracranial neoplasm in children is vomiting. Contrary to common belief, such vomiting is usually not projectile in nature and is often associated with nausea. The initial symptoms, therefore, are often erroneously interpreted as a "gastrointestinal upset," and their underlying cause may go unrecognized for several months. Delay in diagnosis is further enhanced by the fact that the nausea and vomiting are often intermittent in character, occurring every morning for a period of several days, then disappearing and leaving the child in apparent good health, only to recur at a later date in a more persistent form. Several such episodes may occur before an intracranial neoplasm is suspected. Headache, although less constant in children than in adults, is another important symptom of an intracranial neoplasm. Enlargement of the head, strabismus, diplopia, and papilledema are other signs and symptoms common to many intracranial neoplasms, regardless of their location. Localizing symptoms will be mentioned only briefly. In general, posterior midline cerebellar tumors tend to give rise to staggering and uncertainty of gait, the signs of cerebellar dysfunction being most marked in the trunk and lower extremities and being largely the result of a disturbance of equilibrium.[26] Tumors of the cerebellar hemispheres tend to give rise to much more marked cerebellar dysfunction, usually more severe on the side of the tumor, and produce disturbances of voluntary muscular activity in the form of asynergy and slowness of movement, readily manifested by the finger-to-nose and heel-to-knee tests and by the presence of adiadokokinesis.[26] Tumors of the brain stem may not give rise to increased intracranial tension and do give rise to palsies of one or more of the cranial nerves. Because of the

absence of increased intracranial pressure such neoplasms are often misdiagnosed as encephalitis.[26]

The astrocytoma is the most common intracranial neoplasm in children, comprising about 25 per cent of intracranial tumors. In contrast to adults, where such neoplasms occur predominantly in the cerebral hemispheres, in children the vast majority are located in the cerebellar hemispheres or in the vermis of the cerebellum. Grossly they are firm, pale, avascular tumors which may appear to be quite well circumscribed. They may be solid, may contain multiple cystic areas, or may consist of a large fluid-filled cyst with a mural nodule. Histologically they consist of fairly mature astrocytes which may be principally protoplasmic or fibrillary.[28] Numerous fibrils are present between the widely separated cell bodies of the fibrillary astrocytoma; these fibrils may be largely absent in the protoplasmic type.

Cerebellar astrocytomas offer the best prognosis of the intracranial gliomas of childhood. They are generally slowly growing tumors, but tumors involving the vermis may give rise to an abrupt onset of symptoms of increased intracranial pressure and may be indistinguishable clinically from the more rapidly growing medulloblastomas. Simple removal of the fluid from the cavity of a cystic astrocytoma may give relief from symptoms for varying periods of time, but removal of the mural nodule or extirpation of the tumor is necessary in order to affect a cure.

The results in the treatment of cerebellar astrocytomas are truly encouraging. Of twenty patients with cerebellar astrocytomas surgically treated by Bailey, Buchanan, and Bucy, 80 per cent living one to eight years later, the majority of these well, the others with varying degrees of disability, including total blindness.[26]

Medulloblastoma is the next most frequent intracranial tumor of childhood, accounting for 20 per cent of the neoplasms.[27] These tumors are almost exclusively midline cerebellar tumors, usually occurring at a somewhat younger age than the cerebellar astrocytomas[27] and affecting boys more frequently than girls. They comprised 16.2 per cent of 281 gliomas occurring in the military age group.[29] Of all of the tumors of the brain these are the most prone to give rise to multiple implants of tumor tissue in the meninges of the cranial cavity and within the spinal meninges. They cannot always be distinguished clinically from cerebellar astrocytomas involving the vermis, but the rapid progression of symptoms may at times aid in the differential diagnosis.

Histologically these tumors, which arise from the vermis of the cerebellum or the region of the roof of the fourth ventricle, consist of round or oval cells with scanty cytoplasm, usually arranged as a structureless mass but occasionally showing an arrangement of the nuclei in the form of pseudo-rosettes. According to Bailey and Cushing[30] these tumors are derived from undifferentiated cells or medulloblasts and contain numerous spongioblasts and a smaller number of neuroblasts. Roussy and Oberling,[31] however, feel that the predominant element of the tumor is the neuroblast and prefer to classify these tumors as neurospongiomas. Regardless of the origin of these cells, sections from the more

undifferentiated areas may, at least with hematoxylin and eosin stains, be indistinguishable from the highly undifferentiated areas of neuroblastomas or retinoblastomas, tumors also derived from immature neural tissue.

Medulloblastomas are radiosensitive but not as a rule radiocurable. Although their growth may be checked for a considerable period of time by radiation therapy, they ultimately result in the death of the patient.[32]

Ependymomas comprise about 10 per cent of the intracranial neoplasms in children. These tumors usually arise from the floor of the fourth ventricle and give rise to symptoms often indistinguishable from those of the midline cerebellar medulloblastomas. Histologically they are characterized by the radial arrangement of their cells about vascular spaces; the radially arranged nuclei are located at a considerable distance from the central vessel, the intervening region being filled with the processes of the cells. Although these tumors are histologically relatively benign, their location is such that attempts at operative removal carry a high mortality and their ultimate prognosis is poor.

Gliomas of the brain stem constitute approximately 15 per cent of the intracranial tumors of children.[26] Histologically these may show the structure of polar spongioblastoma, astrocytoma, or glioblastoma multiforme. Because of the frequent absence of increased intracranial pressure, these tumors are often erroneously diagnosed as encephalitis. Although many of them are relatively benign histologically, their location makes operative removal impossible.

Malignant tumors of bone feature prominently as a cause of death in later childhood. The majority occur between the ages of 10 and 25 years; males are affected more frequently than females. For practical purposes malignant bone tumors in children may be divided into osteogenic sarcoma and Ewing's tumor of bone. Although these are distinctly different pathologic entities, it must be remembered that clinical and roentgenologic differentiation between these neoplasms is not always possible.

Osteogenic sarcoma usually begins in the metaphyseal region of the long bones, the lower end of the femur and the upper end of the tibia being the sites most frequently involved. The initial symptom is pain, which may be intermittent and nocturnal in character and may precede the clinically palpable tumor by a period of weeks or months. Persistent pain in a long bone should suggest the possibility of a malignant tumor of bone. A history of trauma to the effected part is frequently elicited but it is usually impossible to prove an etiologic relation between trauma and the neoplasm in any given case. Fever may be present, although this is more frequent in Ewing's tumor of bone than in osteogenic sarcoma.

Roentgenologic examination is of inestimable value in the diagnosis of malignant tumors of bone, and frequently a strongly presumptive diagnosis of the type of lesion can be made prior to histologic examination of the neoplasm. However, it is important to remember that the shadows cast by benign lesions of bone may closely simulate those of malignant bone tumors, and a positive diagnosis should not be made and therapy should not be carried out until the true nature of the lesion has been determined by biopsy and histologic examination of the removed tissue. It is as important, moreover, for the pathologist to have the

assistance of a competent radiologist as is the reverse, and erroneous diagnoses may well be made by the pathologist who has not availed himself of the assistance of a competent radiologist or who has not himself examined the roentgen-ray films. Such benign lesions as fibrous dysplasia of bone or even a healing fracture may give a histologic appearance not unlike that of osteogenic sarcoma. The pathologist, then, who takes it upon himself to interpret biopsies from suspected bone tumors, should avail himself of all clinical data pertaining to the case, including the study and interpretation of the roentgen-ray plates.

Much confusion has arisen from the term osteogenic sarcoma, which has been interpreted as referring to a bone-forming tumor. Although some bone production is usually present in such tumors, it is important to remember that osteogenic sarcoma refers to a tumor derived from bone, or, more strictly, a sarcoma derived from ancestors of cells which, when duly differentiated, are known as osteoblasts.[33] These cells may, therefore, cease their differentiation at any point from primitive mesenchyme through the normal sequence of differentiation of bone to fibroblast, cartilage cell, or osteoblast, with resultant variations in the histologic pattern of the tumor. The intercellular matrix may also vary from a myxomatous type of tissue to collagenous, cartilaginous, osteoid, or calcified osseous tissue. Attempts to separate the osteogenic sarcomas into different categories on the basis of their constituent types of cells or matrix, or even on the basis of their gross anatomic location in the bone, are usually of little or no clinical or prognostic value, and the tumors are probably best considered simply as osteogenic sarcomas with a careful gross and microscopic description appended for future reference, study, and conceivably, a more detailed classification.

The treatment of osteogenic sarcoma is amputation, and no more difficult task confronts the pathologist or surgeon than to recommend and carry out amputation in a child often in apparently good health. The task is made even more difficult by realization of the extremely poor prognosis even after amputation. Because of the few recorded five-year survivals in patients under the age of 10 or 12 years who were treated by radical surgery alone or by irradiation alone, Coley[34] recommends a thorough course of preoperative irradiation followed promptly by amputation in young patients (but not in adults).

Ewing's tumor of bone may be indistinguishable from osteogenic sarcoma both clinically and roentgenologically. Characteristically it begins in the shaft of a long bone rather than the metaphyseal region, giving rise to a fusiform enlargement of the shaft. The tumor perforates the cortex, where it stimulates the production of new periosteal bone in successive layers, giving rise to the typical "onion skin" appearance seen in the roentgen ray plate. It should be emphasized that this newly formed bone is reactive in nature, not neoplastic, and that a similar roentgenologic picture can be produced by nonneoplastic conditions. Metastases occur in the lungs, regional lymph nodes, and other bones, so that multiple bone lesions are common at the time of autopsy. This is at variance with osteogenic sarcoma where involvement of more than one bone is rare.

The clinical picture of Ewing's tumor of bone may be confused with that of osteomyelitis, a history of trauma, fever, leucocytosis, and pain being common to both. Even at the time of biopsy differentiation may not be easy, as

the small, dark cells of a Ewing's tumor may be confused with the inflammatory cells of osteomyelitis. Ewing's tumor is characterized by sheets of small, dark-staining, round or slightly ovoid cells with little cytoplasm and no evidence of formation of bone by the tumor cells; mitotic figures may be numerous but giant cells and pleomorphism are uncommon. The histologic appearance may resemble that of neuroblastoma, and indeed Willis[35] feels that many such tumors are actually metastatic neuroblastomas.

Ewing's tumors are radiosensitive but following radiation recurrences often occur and the tumor becomes radioresistant. Amputation or resection immediately following the period of maximum radiation response is probably the treatment of choice,[23] although immediate amputation is carried out by others. Unfortunately, as with osteogenic sarcoma, few five-year survivals can be expected.

No attempt will be made to deal with Hodgkin's disease, lymphosarcoma, and sarcomas of soft tissues, as these neoplasms have their counterparts in adult life. No attempt will be made to cover the subject of leucemia, the most common fatal type of cancer in children, as this is a subject too broad for the scope of the present paper. Suffice it to say that leucemia in childhood is usually of the acute type. The initial symptoms may be those of an acute infectious process, hemorrhagic phenomena, or bone and joint pain which may simulate rheumatic fever. Changes in the peripheral blood are often inadequate for diagnosis, and bone marrow aspiration is probably always indicated before institution of therapy. Recent studies [36, 37] have indicated that Aminopterin and related compounds may produce temporary but significant clinical, hematologic, and bone marrow remissions in patients with acute leucemia. However, the severe toxic effects of these drugs and the fact that they merely produce remissions, not *cures*, must be remembered. Although of value in the treatment of leucemia, their greatest value appears to be toward further research on the fundamental nature of the neoplastic cells.

SUMMARY AND CONCLUSIONS

Malignant disease is one of the most important causes of death in children under 15 years of age. Although in general, malignant tumors in early life carry a very grave prognosis, many cases can be cured by prompt diagnosis and early therapy. Although some forms still have a hopeless prognosis, cure rates in others prove that the defeatist attitude exhibited by so many when dealing with malignant tumors in childhood is not justified.

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Psychologic Aspects of Pediatrics

SELF-REGULATION AND THE MOTHER

HARRY BAKWIN, M.D.
NEW YORK, N. Y.

AMERICAN pediatrics has rejected traditional methods of child rearing and has adopted instead an attitude toward child care which is based on developmental principles. The child's maturing needs and capabilities are to be the guides to management. Each child is viewed as an individual whose pattern of development fits, in a general way only, the development of children as a whole. Training procedures for self-feeding, toilet, etc., are introduced when the individual child is ready to be trained and not according to a prearranged time schedule.

This point of view seems reasonable and sensible. It should make childhood happier, child rearing easier, and, perhaps, prevent a certain amount of emotional difficulty in later life. It is an approach which places the responsibility for making decisions about the child largely on the mothers. They, not the doctor or the book, are to decide, from the baby's behavior, when he is to eat and how much, how long he is to be allowed to cry, when he is to be toilet trained, and so on.

The success of the modern approach depends, to a large extent, on the personality of the mother (as well as that of the child) and her reaction to self-regulation. Unfortunately, there are many mothers to whom the task of individualizing child rearing is a source of great anxiety. Themselves reared according to rigid regimens, they have, perhaps, taken courses in child psychology and read books on the subject, and they are imbued with the idea that bringing up a child is a highly complicated science. Telling them that child rearing is actually a very simple process, carried out successfully by millions of very simple people, pointing out that the most desirable attitudes toward a baby are the unlearned attitudes that adults intuitively assume, urging them to be natural with their baby; these are of little or no avail. Some of these mothers are too young, others too old. Some are overly anxious because of the loss of a previous child, or because of a serious illness or a defect in a previous child or in the child of a near relative or a friend. In other instances, the mother's emotional difficulties are more deep-seated, and parenthood simply gives direction to her inner tensions. But most of them are quite normal as indicated by their much more relaxed attitude toward subsequent children. Unaided by the sanction of a traditional approach, they are overwhelmed by a task which they are, for the time being, unable to handle.

The Department of Pediatrics, College of Medicine, New York University-Bellevue Medical Center.

There are other mothers to whom self-regulation is distasteful. Some have had a certain amount of experience in the business world and derive great satisfaction from receiving precise prescriptions for feeding, sleep, toilet training, etc. (the "orderly type"). Still another group consists of women who are by nature dominating or bossy (the "executive type"). They like to feel themselves in command of every situation. They generally accept the physician's prescriptions calmly and then proceed to disregard them, doing things their own way. They have little difficulty while their children are babies; only later on, when they encounter a child whose emotional make-up is modeled after their own, does the clash of personalities lead to trouble.

In giving advice regarding child rearing, then, the physician must take into consideration the parental personalities, particularly that of the mother. The method of child rearing must suit the maternal temperament and cultural background. Individualization is fully as necessary in dealing with the mother as it is with the child. If the physician is convinced that self-regulation is going to make the mother overly anxious or otherwise unhappy, more or less specific directions should be given. An approach which she finds uncongenial will not only disturb her emotionally, it will make her task more difficult and will probably create unnecessary tensions in the child. It is unwise to try to coerce a mother who, by training, previous experience, or temperament, needs detailed instructions. Insistence that she take on, at once, the full responsibilities implied in motherhood serves only to increase her uncertainty, to undermine her self-confidence, and to lessen her efficiency.

It is well to remember that children reared by methods far different from ours, grow up to be adults who are, according to general observation (the only available standard), fully as happy and stable as we. Every country, every culture, has its own unique way of bringing up children which, in the main, is based on tradition. These different methods are, to a large extent, expressions of national or cultural ideals.

A systematic study of child rearing in certain central and eastern European cultures was recently carried out in New York City by Benedict.[1] In contrast to the current American practice of allowing babies freedom of movement from the time of birth, it is the custom among the peoples of eastern Europe to swaddle babies. Swaddling is tightest and is continued longest in Russia. The bundled baby is kept as rigid as if he were bound to a board. Sometimes the lashing is so tight that respiration is interfered with and strangulation is averted only by loosening the bindings. The swaddling is considered to be necessary for the safety of the infant who is regarded as being in danger of destroying himself. The baby must be confined for his own sake and his mother's. However, he is not isolated. He is kept where adults are congregated and he is talked to and carefully cared for. Swaddling is continued for nine months, sometimes longer.

The restriction does not relate to the emotions, however. Since the baby's principal means of grasping the outside world is through the eyes, it is significant that in Russian speech and literature great emphasis is placed on the eyes, as "mirrors of the soul."

An interesting feature of child rearing in Russia is the diffuseness of relationship between child and adults. The child's contact during the first year of life is not limited to the mother but is spread among many adults such as wet nurses, older women who are engaged to care for the baby, and others. Consequently the theme of mother love is practically nonexistent in Russia. Nursing and toilet training are warm and permissive.

The Polish attitude toward swaddling is quite different from the Russian. The infant is looked upon as fragile, not violent, and the bindings are applied to give the baby support and to keep his legs straight. Swaddling is regarded as the first step in a long process of "hardening"; and since one is hardened by suffering, suffering is also highly prized. Crying is good for a baby because it strengthens the lungs, and beating a child is also good, for it too "hardens" the child.

Another purpose of swaddling in Poland is to keep apart the clean and dirty parts of the body. The binding prevents the baby from putting the toes in the mouth—the feet in Poland are viewed as shame-ridden as the genital organs—and it keeps the baby from touching his face with the fingers which may just before have touched his crotch or his toes.

Whereas weaning is gradual in Russia, the baby receiving chewed bread at an early age and other foods later on while still nursing, the process in Poland is sudden. The Polish baby is not given an opportunity to accustom himself to solid food until he is taken off the breast; the sudden transition is good because it is "hardening."

The Russian custom of having many adults care for the baby is not practiced in Poland. Only the mother can touch the baby without danger of harming him.

Jewish babies in Poland and the Ukraine are also swaddled. The binding includes a soft pillow and the wrappings are rather loosely applied. As she swaddles the baby the mother generally sings to him. The specific stress is on warmth and comfort and the restriction is regarded with pity and commiseration. Swaddling is also viewed as insuring straight legs. It is in no sense considered the beginning of a "hardening" process or as necessary because the baby is inherently violent.

Strange as these customs may seem to us, it is well to keep in mind that, as nearly as one can observe, they have not been psychologically traumatic in the long run. There are many ways of bringing up children. It is becoming increasingly clear that the deviations from the principles of child rearing which we have come to accept are less important, so far as their effects on the child are concerned, than is the state of mind or the general attitude of the parent toward the child. Commenting on Benedict's report, Mead[2] says that too early toilet training, carried out for some casual reason of household management, may have an almost negligible effect on the child, while the same procedure at the proper developmental stage may, because of the emphasis given to it by the mother, be a much greater trauma.

Advice to parents, then, must be tempered by an appreciation of their personalities, their experiences, and their cultural background. This is not

to say that we are to yield readily to mothers who prefer to shift their maternal responsibilities on to the physician. Most of us find it easier to take orders than to make decisions. Parenthood, after all, necessitates taking responsibility and parents will do well to learn this lesson early. But the physician will need to discriminate between those mothers who are ready for self-regulation and those who need the extra support which they get from more or less precise prescriptions.

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Comments on Current Literature

BACITRACIN IN LOCAL TREATMENT OF PYOGENIC INFECTIONS

BACITRACIN, a chemotherapeutic substance isolated from a sporulating bacillus of the *Bacillus subtilis* group,[1] was identified as a diffusable polypeptide possessing antibiotic activity against a variety of gram-positive bacteria and against spirochetes. Early experimental studies in animals showed that bacitracin is absorbed slowly and that it is excreted by glomerular filtration. Its therapeutic potentialities seemed favorable. Further investigations, however, revealed that renal lesions were produced in animals where large doses were administered. Since these toxic renal manifestations were not correlated with the antibacterial potency of different samples of bacitracin, it seemed likely that the toxicity might be due to impurities, and further efforts were made to refine the substance.

In human subjects cautious clinical trials with bacitracin administered systemically gave reasonably good therapeutic results, but here again transient albuminuria and other signs of nephrotoxicity dampened enthusiasm for its general use, particularly in view of the fact that penicillin and bacitracin have an antibacterial spectrum which is almost identical.

However, safe, effective agents for local therapy in pyogenic infections of the skin constitute a real need, and for this purpose bacitracin is proving particularly suitable. Meleney and Johnson[2] in 1947 reported favorable results with bacitracin in the topical treatment of 100 cases of surgical infection, including a variety of types. Solutions or ointments containing 10 to 100 units of bacitracin per milliliter were used. Eighty-eight per cent of these infections responded to treatment, even when some of the gram-positive organisms isolated from the area were shown by culture studies to be penicillin-resistant streptococci or staphylococci.

More recently Miller, Slatkin, and Johnson[3] have reported the results of a careful evaluation of bacitracin in local treatment of pyogenic infections. Various base preparations were used as ointments, containing varying concentrations of bacitracin. In the laboratory and clinical appraisal of these preparations three features were considered: the physical properties of the base preparation, the stability of the antibiotic when incorporated in the ointment, and the release of the bacitracin content. Of fourteen ointment bases tried, three were definitely superior:

Base No. 2	Carbowax 1540	50 Gm.
	Carbowax 200	50 Gm.
	Carbowax 4000	25 Gm.
Base No. 8	Cetyl alcohol	10 Gm.
	Glycerin	10 Gm.
	Sodium lauryl sulfate	1 Gm.
	Distilled water	74 c.c.
Base No. 10	Lanette wax	20 Gm.
	White petrolatum U.S.P.	20 Gm.
	Liquid petrolatum U.S.P.	30 c.c.
	Distilled water	30 c.c.

Bacitracin was added to each ointment base, 500 units per gram being incorporated in some samples and 1,000 units in others. The ointments remained stable and therapeutically effective for at least two weeks without refrigeration. By laboratory tests oil-in-water and greaseless carbowax bases were found best for stability and for release of bacitracin.

The majority of the patients studied were seen in the Outpatient Clinic. In all cases bacterial cultures of the lesions were taken before treatment in order to identify the causative organism and test its sensitivity to bacitracin. Of sixty-eight patients treated for primary superficial skin infections, fifty responded favorably. In eighteen patients, eleven of whom had folliculitis of the beard, the therapeutic response was unsatisfactory. However, in six of these so-called failures, all of whom had folliculitis of the beard, the infection was kept under control and the area free of lesions so long as the ointment was used daily. The remaining seven instances of failure included one case of infectious eczematoid dermatitis, three cases of vesiculopustular eruption of the hands, one folliculitis elsewhere than of the beard, and two cases of perifolliculitis capitis.

Another group included in this outpatient study comprised patients with dermatoses complicated by secondary bacterial infection. While the secondary bacterial infection was cured in this group, bacitracin ointments were of no value against the primary dermatoses.

No better clinical results were obtained in any of the cases with ointments containing 1,000 units of antibiotic per gram than with those containing 500 units per gram.

On the basis of their experience the authors conclude that bacitracin is an effective agent for local therapy in pyogenic infections of the skin. Its effectiveness approximates that of penicillin, the sulfonamide drugs, and nitrofurazone, and its real superiority consists in the low rate of sensitization of the patient, one-half of one per cent sensitization being recorded thus far. This situation is in contrast to the findings with penicillin where 6 per cent of patients were sensitized, and with sulfonamides and nitrofurazone, where 5 per cent were sensitized to the drugs. No cutaneous reactions to bacitracin have been reported. In one patient this antibiotic in ointment form was applied daily for 300 days with no evidence of cutaneous sensitization.

While bacitracin is toxic when administered parenterally, this is not the case apparently when it is used as a local therapeutic agent, even where the ointment is applied over widespread areas of the body surface. If more evidence is added that such is the case and that sensitization on prolonged use is minimal, the advantages of local bacitracin are obvious. Where patients develop sensitization to other agents such as penicillin and sulfa drugs, and particularly where the causative organisms become resistant to these medications, bacitracin may be of considerable importance in the local therapy of skin infections.

RUSSELL J. BLATTNER.

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CHARLES ANDERSON ALDRICH
1888—1949

In Memoriam

CHARLES ANDERSON ALDRICH
1888-1949

CHARLES ANDERSON ALDRICH died Oct. 6, 1949, at his home in Rochester, Minn., after an extended illness. He was born at Plymouth, Mass., March 4, 1888. He received his Bachelor of Science degree from Northwestern and his Doctor of Medicine degree from the medical school of Northwestern in 1915 and interned at the Evanston Hospital and the Nursery and Children's Hospital in New York. In 1917 he started private practice and in 1921 took graduate work at Harvard in pediatrics. From 1921 to 1941 he was in active pediatric practice in Winnetka, Ill. In 1941 he retired from private practice to become chief of staff of the Children's Memorial Hospital in Chicago, where he remained until 1944 when he took over the directorship of the Rochester Child Health Project of the pediatric department of the Mayo Clinic. He was on the pediatric staff of the Evanston Hospital from the time he started practice to 1942, and was on the staff of the Children's Memorial Hospital in Chicago from 1921 until he gave up the directorship in 1944. He was a member of the teaching staff of the medical school of Northwestern from 1921 to 1944 and received his professorship in 1935. While in Winnetka he was active in community life and was on the Board of Education and a trustee of the North Shore Country Day School.

He was an active member of a number of medical societies and was chairman of the Section on Pediatrics of the American Medical Association in 1930. He served on the Council of the American Pediatric Society from 1935 to 1942 and was president in 1944. He was secretary of the American Board of Pediatrics from its founding in 1932 to 1944, and was president from 1945 to 1947. He was a member of the Editorial Board of the JOURNAL OF PEDIATRICS from 1941 to 1947.

In his earlier years he contributed a number of scientific articles to pediatric literature, of which his studies on nephrosis are perhaps best known. His interest in later years was in correlating child development and child psychology with the problems of pediatric practice. In 1929 he published his first book, *Cultivating the Child's Appetite.* In 1938, in association with Mrs. Aldrich, *Babies Are Human Beings* was published, which deservedly has gone through many editions and is a pediatric classic. In 1941, again with Mrs. Aldrich, *Feeding Our Old Fashioned Children* was published. For the influence of these books and for his studies on child behavior, he received the "Medal" of *Parent's Magazine,* and in 1948 the Lasker Award.

Perhaps his major interest in his long and productive career in the field of pediatrics was the task in which he had been deeply engrossed up to the time of his final illness—that of organizing, directing, and planning the unique research project in child health at Rochester.

In 1916 he married Mary McCague, who was associated with him in writing his last two books. He is survived by Mrs. Aldrich and three children, Robert A. (a physician), Cynthia, and Stephen.

B. S. V.

News and Notes

The following were certified by the **American Board of Pediatrics** at the examination held at Brooklyn, N. Y., Oct. 21, 22, and 23, 1949.

Dr. Jerome Seymour Beloff, 213 East Main St., Meriden, Conn.
Dr. Thomas D. Benson, 4210 St. Paul Blvd., Rochester, N. Y.
Dr. Sydney Borow, 3400 St. Vincent St., Philadelphia 24, Pa.
Dr. Philip Briscoe, 212 Prince George, Annapolis, Md.
Dr. John Brandon Castiglione, 222 West Willow St., Visalia, Calif.
Dr. Albert Cohen, 299 Broadway, Cambridge, Mass.
Dr. Peter Alexander Duncan, 264 King St., Port Chester, N. Y.
Dr. Samuel E. Elmore, Jr., 157 Pine St., Spartanburg, S. C.
Dr. Harold Y. Finck, 2912 Naylor Rd., S.E., Washington, D. C.
Dr. Martin Harwin, 65 Lenox Rd., Brooklyn 26, N. Y.
Dr. Frederic Hertzmark, 976 Blue Hill Ave., Dorchester 24, Mass.
Dr. Martin H. Jacobs, 96-14 63rd Dr., Forest Hills, N. Y.
Dr. Frank W. Kibbe, Lincolnville, Me.
Dr. Robert Koenigstein, Sea View Hospital, Staten Island, N. Y.
Dr. Steven Ellis Koweity, 100 Madison Ave., Franklin Square, L. I., N. Y.
Dr. Margaret Morgan Lawrence, 33-11 107th St., Corona, N. Y.
Dr. Fernando R. Leyva, 1832 K St., N.W., Washington, D. C.
Dr. Laura L. Lipscomb, 663 W. Peachtree St., N.E., Atlanta, Ga.
Dr. Herman Lubenstein, 1585 White Plains Rd., Bronx, N. Y.
Dr. Harold S. Medoff, Hospital of the University of Pennsylvania, Philadelphia, Pa.
Dr. Thomas M. Monagan, 195 Grove St., Waterbury, Conn.
Dr. Irving Nelson, 150 E. Hartsdale Ave., Hartsdale, N. Y.
Dr. Arnold Paul Nicosia, 348 Park Ave., Munsey Park, Manhasset, L. I., N. Y.
Dr. George Saxon Palmer, 110 South Duval St., Tallahassee, Fla.
Dr. Charles Frank Payton, 611½ South Washington, Royal Oak, Mich.
Dr. Louis Arthur Perillo, 638 Amboy Ave., Perth Amboy, N. J.
Dr. Gerald J. Piserchia, 379 Washington Ave., Belleville, N. J.
Dr. Alexander Randall, 133 South 36th St., Philadelphia, Pa.
Dr. Arthur J. Rich, 7945 Riverton Ave., Sun Valley, Calif.
Dr. Homer R. Rich, 227 Kiesel Bldg., Ogden, Utah.
Dr. Joseph Robinson, 76 West Union St., Wilkes-Barre, Pa.
Dr. Sydney Ross, 2440 16th St., N.W., Washington 10, D. C.
Dr. John J. Ryan, 20 Faneuil Road, Waltham, Mass.
Dr. Steven Sawchuk, 3701 North Broad St., Philadelphia 40, Pa.
Dr. Charles Frederick Scholhamer, 116 Avon St., New Haven, Conn.
Dr. Frank W. Shaffer, 1451 DeKalb St., Norristown, Pa.
Dr. Robert Traill Shipman, 907 Summit Ave., Jersey City 7, N. J.
Dr. Leslie Byron Silverstine, 53 School St., Bradford, Pa.
Dr. S. Harvey Sklar, 647 Anderson Ave., Cliffside Park, N. J.
Dr. Jack M. Spitalny, 225 Lancaster St., Albany, N. Y.
Dr. Frederick Harris Stiefel, 373 Ocean Ave., Brooklyn, N. Y.
Dr. Ralph S. Stiller, 1633 Ripon Pl., Alexandria, Va.
Dr. Henry Herbert Stroud, 1017 Park Pl., Wilmington, Del.
Dr. Edward Sydney Szelewa, 87 Stuyvesant Ave., Newark, N. J.
Dr. Henry C. Thacher, 11 Turner St., Auburn, Me.
Dr. Charles Varga, 303 East 20th St., New York 3, N. Y.
Dr. John T. Walke, 303 Washington, S.W., Roanoke, Va.
Dr. Alvah Marvin Weiss, 953 Paulding St., Peekskill, N. Y.
Dr. William Hoge Wood, Jr., 308 E. Market St., Charlottesville, Va.

The **American Academy for Cerebral Palsy** announces that its annual meeting will be held in New York City at the Waldorf-Astoria Hotel on Friday and Saturday, Feb. 17 and 18, 1950, immediately following the meeting of the American Academy of Orthopaedics.

Scientific sessions will be open to visiting orthopedic men and any other physicians interested in the problem of cerebral palsy. These sessions will be on Friday, February 17, from 2 to 5 P.M., and on Saturday morning, February 18, from 9 A.M. to 12 noon. All phases of cerebral palsy will be discussed.

University of California Medical School is offering graduate and postgraduate courses in 1950 at the Medical Center in San Francisco. Postgraduate courses on Special Problems in Pediatrics will be held February 6 through February 10.

Five authorities in specialized fields of maternal or child health have been appointed part-time consultants to the Division of Health Services of the Children's Bureau. While continuing their present positions, they will, from time to time, work with state health officers as requests are directed to the Children's Bureau. The consultants are as follows: Dr. Harry H. Gordon, Denver, for consultation on programs for premature infants; Dr. William G. Hardy, Baltimore, for hearing and speech problems; Dr. Meyer A. Perlstein, Chicago, for problems in the field of cerebral palsy; Dr. Grete L. Bibring, Boston, in developing maternal and child health programs; Dr. John Whitridge, Jr., Baltimore, for obstetric services, particularly in rural areas.

A written examination of the **American Board of Pediatrics** will be held in various cities on Jan. 12, 1950.

A series of Laboratory Training Courses will be given from January through the year 1950 by the **Communicable Disease Center of the Public Health Service**, Atlanta, Ga. The courses will vary from one to three weeks in length and over twenty courses will be given. Full details can be obtained from the Chief, Laboratory Division, Communicable Disease Center, 291 Peachtree St., N.E., Atlanta, Ga.

The International and Fourth American Congress on Obstetrics and Gynecology will be held at Hotel Statler in New York on May 14 to 19, 1950. Dr. Howard C. Taylor, Jr., of New York, is chairman of the Program Committee. Details regarding the meeting can be obtained through Dr. Fred L. Adair, 161 East Erie St., Chicago 11, Ill.

Book Reviews

New Gould Medical Dictionary. Edited by Harold W. Jones, M.D., Normand L. Hoerr, M.D., and Arthur Osol, Ph.D., Philadelphia, 1949, The Blakiston Company, 1,294 pages. Price $8.50 (thin paper edition, $10.75).

This is a completely new reference book in which the editors were assisted by 100 contributors, in large part from the Western Reserve Medical School, covering all the various subfields of medical specialties. A new system of pronunciation is used by syllable and accent and the principle followed of recording pronunciation in actual current use. The type is clear and easy to read. The biographic entries are far from satisfactory as, for example, Abraham Jacobi has been omitted while many names of much less importance are included. Recent pediatric literature has been somewhat overlooked. For example,

under "test" we find no mention of "Coombs test," and under the heading of "solutions" no reference to "Hartmann's solution" which has been in common use for a number of years.

A Boy Grows Up. Harry C. McKown, New York, 1949, McGraw-Hill Book Company, Inc., 312 pages Price $2.40.

This book, written by an educator, is full of advice, rules, and inspiration for the adolescent boy. Unfortunately this approach to the problems of growing up has been tried and found wanting (even Horatio Alger has lost his appeal). There is a place for this kind of approach but it should be coupled with a deeper appreciation of the feelings and emotional problems of the adolescent. This book nowhere approaches such an understanding and would certainly not conform to our present-day concept of "guidance."

WARSON.

A Child's Eyes. Richard G. Scobee, M.D., St. Louis, 1949, The C. V. Mosby Co., 109 pages. Price $2.00.

This small volume is a discussion of vision and the eyes of the young child with particular reference to crossed eyes, their causes, types, and treatment. As the author states in the foreword, it is written primarily for parents, and hence a pediatrician was selected for the review. It is far too complex and technically written to help any but a most highly educated parent in understanding the background and treatment of crossing. On the other hand, it is of interest to, and should be of great help to physicians and pediatricians in understanding vision in young children. The reviewer, for example, gained a much better understanding of the subject than he had held before, and for this reason it can be recommended to the practicing doctor whose knowledge of optics is likely to be rather sketchy. As to its technical accuracy, the reviewer was assured by two well-known ophthalmologists that the text is sound.

Illustrated Handbook of Simple Nursing. Wava McCullough, assisted by Marjorie Moffit, R.N., New York, 1949, McGraw-Hill Book Company, Inc., 239 pages. Price $3.00, 20 per cent discount to teachers and schools.

This is one of the most interesting, unique, and practical books that has reached this reviewer's desk. The author during the war was on the staff of the United States Office of Education and was assigned to study the methods used in training attendant nurses, and this text for the instruction of beginners is the result. It differs from all others in that it utilizes the visual method of instruction which came into such prominence during the war when large numbers had to be rapidly trained in skills. Each task that the nurse has to carry out is illustrated by clever drawings by the author which visualize the point of the accompanying text. There are ten chapters, of which the first three deal with the care and comfort of the patient. The next four take up therapeutic and medical procedures, and the last three chapters consider the convalescent, feeding, and emergencies.

While it is stated that the purpose of the book is for the instruction of nurse attendants in simple nursing procedures, in the opinion of the reviewer it will have a much greater field of usefulness. It should be of great help in training nurses aides and in home nursing courses such as those of the Red Cross, and, in addition, it is a book that will be most useful on the shelf of the home library. We are further confident that the sections on the care of the patient could be read with profit by a large majority of the graduate nurses we have worked with over the years. It is a book on nursing with which the practicing physician should be familiar and one we intend to recommend to mothers.

B. S. V.

Editor's Column

"ANDY" ALDRICH

ON another page of this issue are the abbreviated biographic data of the active and useful life of one of the finest leaders in the development of modern pediatrics. To have known and been associated with Andy Aldrich, with his keen mind, his gentleness, his tolerance, his sense of responsibility to his patients and to his colleagues, was a privilege, as many will testify. He had the inquiring mind of the true scientist. In his earlier years, in spite of the demands of a busy practice, he found time to make careful clinical studies which would have been a credit to any "full-time" research department. His unique contribution, however, was the questioning of the problems of growth and development which arose in the routine of his everyday practice, and their solution. His philosophy, based on his experience in practice, was that "attitudes" on the part of parents in their relationships with their children are more important than "details," which was the basis of most pediatric thought some twenty years ago. This philosophy and his attitude to those under his care was well expressed in the title of his most important book, *Babies Are Human Beings.* In addition, he found time to take an active part in the life of the community in which he lived and to contribute much to its welfare. Only those of us who were associated with him in the early days of the "Board" know how much he was interested in and gave to the development of the younger man in pediatrics. He was an outstanding example of the maxim—that if you want something done, select the busy man. We believe that the historical perspective of future years will look upon him as having been one of the outstanding influences on the pediatric thought and practice of his generation.

To the younger pediatricians who subconsciously must have some ideal to pattern themselves after, his life, his work, and his medical accomplishments offer a goal well worthy of emulation.

Andy Aldrich will be greatly missed by his many friends in the pediatric world.

AUREOMYCIN IN PANCREATIC FIBROSIS

SATISFACTORY results from the use of aureomycin in the treatment of pulmonary involvement in pancreatic fibrosis have recently been reported by Schwachman and his co-workers* from the Children's Medical Center in Boston. In a series of thirty-five cases treated from two to four and one-half months, the response was excellent in thirty-one. The cough disappeared and there was a gain in appetite and body weight. The dosage used was from 20 to 30 mg. per kilogram of body weight in divided or single daily doses. Relapses, however, almost invariably occurred when the drug was discontinued.

*Schwachman, Crocker, Foley, and Patterson: Aureomycin Therapy in the Pulmonary Involvement of Pancreatic Fibrosis, New England J. Med. 241: 185, 1949.

One of the most interesting observations was that nausea and vomiting were rarely encountered in the patients, and that there was a decided change in the character of the stools accompanied by gain in body weight. About one-half of the patients in the series were under 2 years of age. In a recent report on a series of 134 cases of pancreatic fibrosis in THE JOURNAL by May and Lowe,* the authors reported the clinical impression that the pulmonary involvement in pancreatic fibrosis had its inception shortly after birth and reached its intensity between 6 and 18 months of age. Further, that in children surviving this period, the intensity seemed to subside, and that children living 5 to 8 years are often almost free of pulmonary complaints. Aerosol antibiotic therapy, which has been used recently for the pulmonary lesions, is a difficult and far from satisfactory method of treatment in infants and young children. Hence the experience of the Boston group with orally administered aureomycin seemingly offers a decided advance in the therapy of the condition.

*May and Lowe: Fibrosis of the Pancreas in Infants and Children, J. PEDIAT. 34: 663, 1949.

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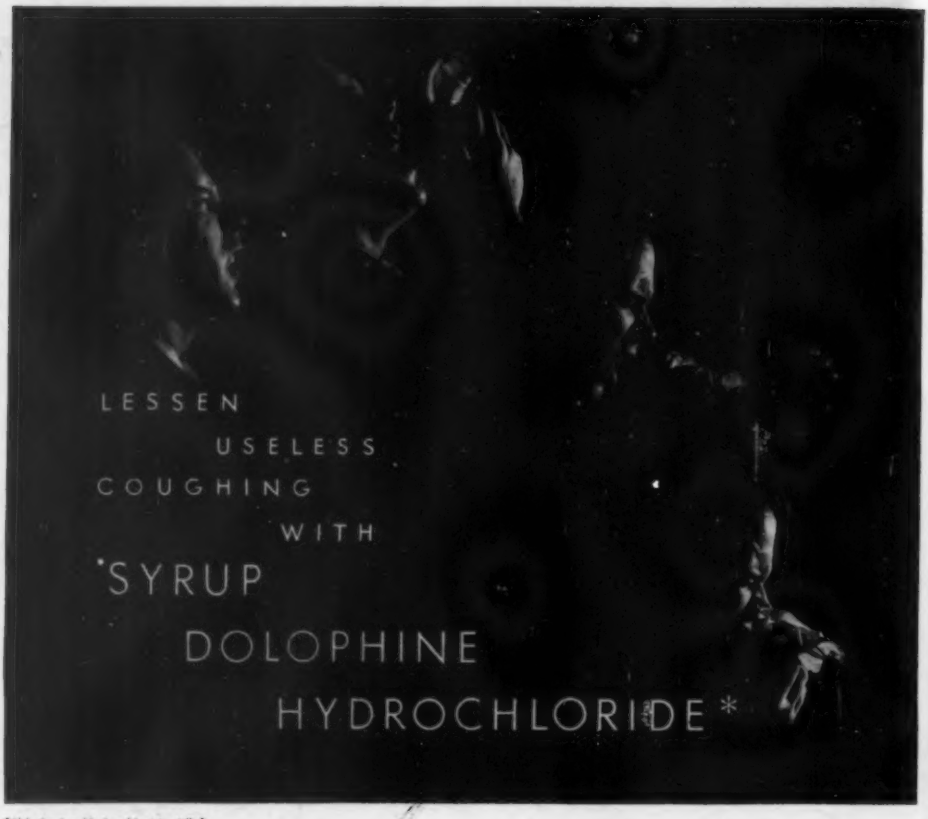

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